AMERICAN HEART JOURNAL

AN INTERNATIONAL PUBLICATION FOR THE STUDY OF THE CIRCULATION

VOLUME 53

JANUARY-JUNE, 1957

ST. LOUIS

THE C. V. MOSBY COMPANY

1957

VOLUME 53

Printed in the
United States of America

VOL. 53 JANUARY, 1957 No. 1

AMERICAN HEART JOURNAL

AN INTERNATIONAL PUBLICATION FOR THE STUDY OF THE CIRCULATION

Contents on Inside Cover

American Heart Journal

CONTENTS FOR JANUARY, 1957

Editorial

Original Communications

Clinical Reports

Book Review

Announcement

(*Editorial and Business Communications on Page 2 of Advertising Section*)

Vol. 53, No. 1, January, 1957, American Heart Journal is published monthly, by The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis 3, Missouri, entered as second-class matter January 23, 1917 at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Additional entry authorized at Jefferson City, Missouri. Subscription rates: United States and Its Possessions $13.00, Students $6.50; Canada, Latin-America, and Spain $13.50, Students $7.00; Other Countries $14.50, Students $8.00. Single copies, $2.00 postpaid. Printed in the U. S. A.

American Heart Journal

VOL. 53 JANUARY, 1957 NO. 1

Editorial

NEW YEAR'S GREETINGS AND FRAGILE RESOLUTIONS

AT THIS time of the year, it is a pleasant custom to wish our friends happiness and prosperity in the future. This I do, and I know that I am joined by the Editorial Board of the American Heart Journal in sending good wishes for 1957 to our past and future contributors.

It is also the season when good resolutions are made, whether or not they are to be kept. Unfortunately our human frailties lead in time to the temptation to forget why these good resolutions were made and to return to the sins of the past. It is with reference to these hoped-for virtues and the relapses into sin that I wish to deal at present.

In the composition of any journal, there are two parties: the contributor and the editorial board. As both of these occupy a definite function of time, I will consider them in that order.

The construction of a manuscript which will be clear and appealing to the reader is the duty of the contributor. However, many authors seem to think that verbosity is a primary virtue. To the reader this is a primary sin. The latter takes strong objection to reading articles in which repetition without justification is a prominent feature. It probably would be well to take up in logical sequence the various divisions of a well-constructed manuscript.

The introduction should state clearly, in simple language, what prompted the writing of the manuscript. This should be done in one short paragraph, and the intimation of final results should not be indulged in for it leads, in many instances, to an anticlimax which is not justified by the eventual findings, or in other cases, it anticipates future speculations.

The methods employed, if they are original, should be described concisely and clearly. If, however, they are adopted from previous publications, a simple reference should be made to the original article. If, in addition, there are modifications, these should be stated briefly. In dealing with the material employed, it is of the utmost importance that the controls be sufficient in number, and that they be comparable, as far as is humanly possible, with the material upon which the essence of the manuscript rests. It is appreciated that this may often be difficult to accomplish, but if the controls and the observed deviations from normal are not sufficiently comparable, the whole fabric of the manuscript stands upon a false basis, and speculation, which might be called an original sin, domi-

nates the conclusions. The description of the material upon which the article rests should be concise, and all superfluous details should be eliminated. It should not be necessary to give all the details of a blood count, the urinary findings, the examination of stools, electrocardiograms, and x-rays unless in these there is some feature pertinent to the subject under discussion. It is quite sufficient to state that these are normal. The common phrase that they were "not remarkable" evades the issue, and "remarkable" is a word that should be removed from the medical vocabulary. It is true that subsequent events may show a variation in these normal findings, in which case it is quite proper that the original determinations be given in some detail. The same criticism may be directed toward the description of autopsy findings. These should be set down in meticulous detail as regards the abnormal changes, but they should not be submerged in a mass of normal descriptions of other organs and tissues.

It is not within our purpose to go into details of specific decisions. The general principles are there to be followed.

The discussion of the findings is often the "bête noire," not only of the committees of referees of the Editorial Board but also of many readers. Long comparisons with other findings frequently lead nowhere, and there is apt to creep in a large element of speculation when the author seems to confuse "the wood for the trees." In such circumstances, it is not surprising that the reader also becomes completely bemused. If there is well-founded evidence that the findings recorded appear to be at variance with previous concepts, this should be stated in clear and concise language and the reader be allowed to form his own conclusions. When it comes to a summary, this is in most cases unnecessary if the description has been to the point. On the other hand, the author's conclusions should emphasize the salient points and, by avoiding too much repetition, leave the reader with a clear-cut idea of the author's opinions with which he may or may not agree.

I do not wish it to be inferred from the above that the Editorial Board is like Bayard "without reproach." The American Heart Journal has often been over-generous in accepting manuscripts which were unduly long in spite of the fact that many of these were returned to the authors for condensation, the motto being "Brevity without loss of clarity." This applies not only to the text but also to the number of illustrations which frequently are repetitious and confusing without adding virtue to the article. Striking graphs are often an improvement on elaborate tables particularly if the latter are so large and made up of so many irrelevant columns as to make it difficult for the reader to decipher them. If necessary, such tables may be published as appendices to the paper.

Those who have had experience in reading theses for advanced degrees can usually detect manuscripts which have served as such. The detection is particularly simple when in the discussion there are pages upon pages of references to past publications whether these be purely relevant or not. In a thesis, such an analysis of the literature is, of course, an index to the author's industry and erudition. It must be acknowledged that many theses for advanced degrees are of excellent caliber but they are far too often relegated to departmental archives. It seems that there should be some means whereby the best of these

could be published in their entirety, as occurs, to cite some examples, in the supplements to the various "Acta," the theses of the University of Paris, and so on.

Finally, I would make a plea that authors read carefully the instructions dealing with "Manuscripts" on Page 2 of this JOURNAL. If they would follow these counsels they would save many headaches and heartaches for themselves, the editorial staff, and the typesetters.

Although I may seem to be critical, and to some perhaps unjustly so, and should not be the one to cast the first stone, I would like to revert to the first paragraph and repeat our good wishes for 1957, at the same time hoping that any good resolutions prompted by later paragraphs will not fade into oblivion after February 1.

THE EDITOR

Original Communications

SOME PHYSICAL ASPECTS OF BLOOD PRESSURE, PULSE WAVE, AND BLOOD PRESSURE MEASUREMENTS

L. H. VAN DER TWEEL, D.SC.

AMSTERDAM, HOLLAND

INTRODUCTION

THE study of the phenomena of blood pressure and pulse propagation gives a good opportunity for physical analysis. Therefore many treatments of the problem have been given in which formulae were deducted for the propagation of pressure waves in elastic tubes and also another number in which the subject was treated more qualitatively. Electrical models in different orders of complication have been considered. All this resulted in many contradictions and also some facts have not been clearly recognized. On request of Professor Snellen of the University of Leyden I have tried to give in the subsequent paper a comprehensive treatise of the subject which, as I hope, will enable also the nonphysicist to understand the essential features in question. The problems connected with the study of blood pressure in arteries (e.g., the aorta) can only be roughly approximated, since there are so many factors owing to the complicated physiologic structure. Therefore a strict mathematical analysis seems not indicated.

First, we shall consider the blood pressure to be static, i.e., the same pressure pulse occurs everywhere in the whole system at the same time. An electrical analogue will be used. After that the dynamic qualities of the system will be introduced. Pulse propagation will be compared with the propagation in electrical cables.

The propagation characteristics are about the same as in catheters used for pressure measurements, and in Part III a method will be described for "damping" catheter reflections. This way of damping used by Professor Snellen and Dr. Rodrigo at the University of Leyden is published elsewhere.[1] For better comprehension we give here a list of analogous electrical and hydrodynamic quantities.

From the Laboratory of Medical Physics, University of Amsterdam, Amsterdam, Holland.
Received for publication Jan. 19, 1956.

Electrical		*Hydrodynamic*	
potential	V	pressure	P
inverse of the capacity	$1/C$	volume rigidity	E
charge	Q	volume	vol
current	$i = \frac{dQ}{dt}$	flow	$f = \frac{d\ \text{vol}}{dt}$
inductance	$\dot{L}$	analogue	$\frac{\rho L_e}{\pi r^2}$ (L_e, length; r, radius of the tube; ρ, specific weight of the liquid)

PART I. BLOOD PRESSURE

Systolic and Diastolic Pressure.—The most drastically simplified electrical model of the left ventricle, the arterial system, and the periphery is that of a current source rapidly charging a condensor, which discharges through a resistance; a recurrent process (Fig. 1). Translated into medical terms: in approximation the ventricle injects the blood into the aorta against any force that may be present. If the aorta should be clamped the pressure would rise infinitely. The arterial system is compared with a condensor. In this simplified model the pressure is the same at any moment throughout the whole system. The periphery is considered a pure resistance, i.e., without elastic properties; the capacity of the arterial system is inversely proportional to the volume rigidity (a better term than volume elasticity as is commonly used) defined by $\Delta P = E \cdot \Delta$ vol. Because of our assumption that the heart is a current source, blood (electrical charge) can never flow back so that valves are not needed. It is clear that this picture is very rough.

The total charge Q that condensor C is receiving at each beat gives a potential difference $V = Q/C$. The condensor discharges through the resistance R, so

TABLE I. SYSTOLIC AND DIASTOLIC PRESSURE AS A FUNCTION OF DIFFERENT CHARACTERISTICS

	V_S	V_D
Normal	120	80
(R) —— 2 R (t_H) —— ½ t_H	215	175
(C) —— ½ C	144	64
(C) —— ¼ C	215	55

The change for the systolic pressure (V_S) and the diastolic pressure (V_D) is given when one of the parameters is changed. When peripheral resistance increases or the frequency increases both pressures rise, but the stroke volume remains a constant. When the capacity (volume rigidity) decreases (as in sclerotic cases) the systolic pressure rises and the diastolic pressure falls.

$V_t = V_S \exp(-t/RC)$ (V_S systolic "potential"). After a time t_H (60/freq.) there is a new injection. At this time the potential (blood pressure) has fallen to the diastolic value $V_D = V_S \exp(-t_H/RC)$.

The difference between diastolic and systolic potentials is Q/C, thus $V_S [1 - \exp(-t_H/RC)] = Q/C$ giving the result:

$V_S = Q/C [1 - \exp(-t_H/RC)]$ and $V_D = V_S - Q/C$, in mechanical terms: $P_S = E \cdot \text{vol}/[1 - \exp(-t_H \cdot E/R)]$, $P_D = P_S - E \cdot \text{vol}$, in which vol = stroke volume.

It follows that an increasing resistance and a decreasing t_H, i.e., an increasing frequency (stroke volume being kept constant), have the same quantitative effect on P_S and P_D, because $P_S - P_D$ is a constant. Increasing of E (a greater rigidity of the system) gives an increasing P_S and a decreasing P_D. The average flow (current) does not change, so the average pressure (voltage) is a constant.

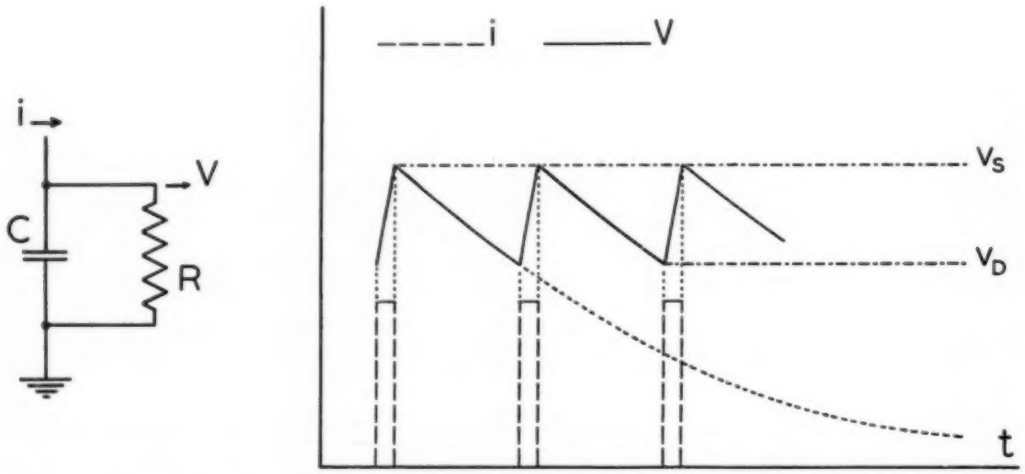


Fig. 1.—A current impulse is sent during each "beat" into the system resulting in a potential course as given in the graph.

The systolic and diastolic pressures in this case must run in opposite directions and because of the exponential (Fig. 1) P_S will rise more than P_D will fall (of course physiologic regulation is not taken into account). We must however consider the fact that E is not a constant as was assumed so far. In normal cases E will have a slight tendency to decrease with rising pressure as long as the pressure is low. In sclerotic conditions, when E is already high, the rigidity will increase significantly with increasing pressure; the same applies to normal cases if the pressure is increasing so much that the nonlinearity of the arterial walls is going to exert its influence.

In the theoretical linear case when the rigidity coefficient of the wall (not to be confused with the rigidity of the whole system) is a constant, we find for the volume rigidity $E = K \cdot \text{vol}^{-3/2}$, in which K is a function of the rigidity of the

wall, which would mean that the system is rapidly growing less rigid at higher pressures. Wiggers[2] assumes that the decrease of the rigidity with pressure follows the law $E = K \cdot \text{vol}^{-1}$, but the experimental data of Hallock and Benson[3] show that nowhere in the physiologic conditions does the rigidity decrease appreciably with pressure. Therefore, we believe that our model, being a simple one, is preferable as it is easily adaptable to particular cases. No big changes are to be expected when the length of the systole or the dynamic characteristic of the system are taken into account. A short table (Table I) gives the changes resulting from varying conditions. Only a change in stroke volume or rigidity gives a change in the pulse pressure. It is very instructive to demonstrate the influence of the various factors with an electrical model on a cathode ray oscillograph.

PART II. PULSE PROPAGATION

A. The Pulse (Fundamental Description).—The assumption that the pressure is spread instantaneously throughout the system enabled the above mentioned simple evaluation. In reality, when systolic ejection starts, the aorta expands and the pressure rises rapidly. When the systolic flow has reached its top value and is assumed to be constant (as an approximation) the pressure stays constant; meanwhile the expansion propagates with a certain velocity. At the end of the systole a big part or the whole of the aorta is expanded and reflections from branches may already have occurred.* From the propagations of this impulse and reflections which may possibly occur we must try to understand the well-known wave forms at different points of the aorta. V. Hardung[4] gives a very clear and comprehensive description of damping and reflection of pressure impulses in the big arteries and reaches the conclusion that such reflections are not important. Hamilton[5] gives a recording which strongly suggests reflections at the femoral side of the aorta. We shall discuss these points later on.

The transmission of a pressure impulse through an elastic tube may be compared with the transmission of an electrical impulse through a cable and must not be confused with the normal flow of blood itself. In the latter case the blood is moving through the system. In the former case, when there is no superimposed stationary flow, the pressure pattern is moving, the movement of the particles being restricted to only a small area.

Electrical transmission has been studied extensively; therefore we use the electrical analogy with advantage. Many treatments have been given on impulse propagation, simple and complicated ones. A study of the latter type is that by King,[7] but for our purpose we prefer a simpler model.

Suppose we had a cable with capacity c and an inductance l per centimeter length, then for the mechanical case the relations are $c = 1/E_S$, $l = \rho/\pi r^2$ (explained later on) where ρ is the specific weight of the liquid, r the radius of the

*In a paper in which a very efficient method for measurement of conditions in wave propagation is given, Peterson[6] does not recognize the importance of these dynamic characteristics. If an impulse of flow is sent into an elastic tube the pressure rises instantaneously and does not overshoot, as would follow from Peterson's analysis in which he makes a distinction between acceleration and elastic forces, which is not admissible under these circumstances. The first peak in his Fig. 6 may already be due to reflections.

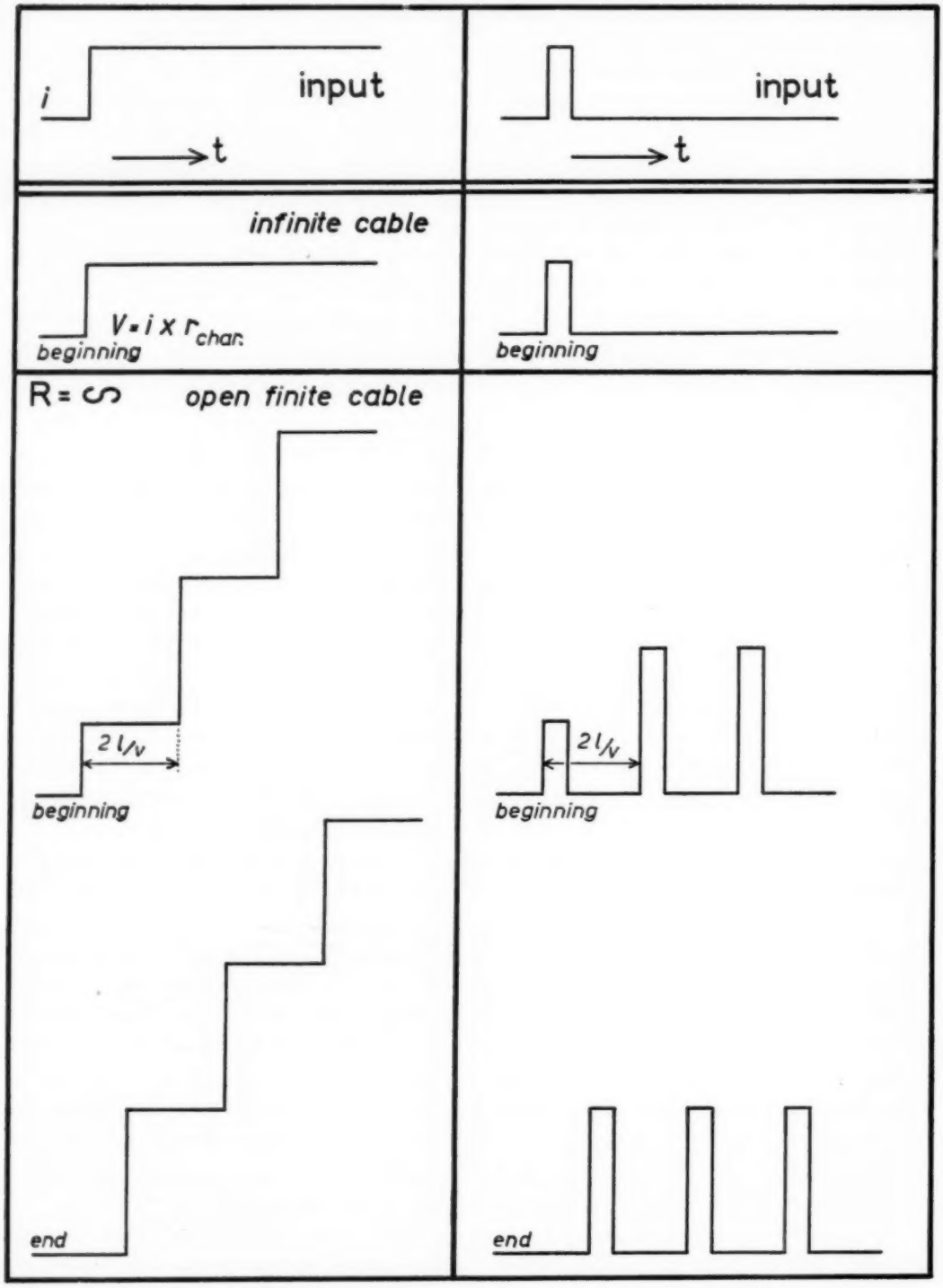
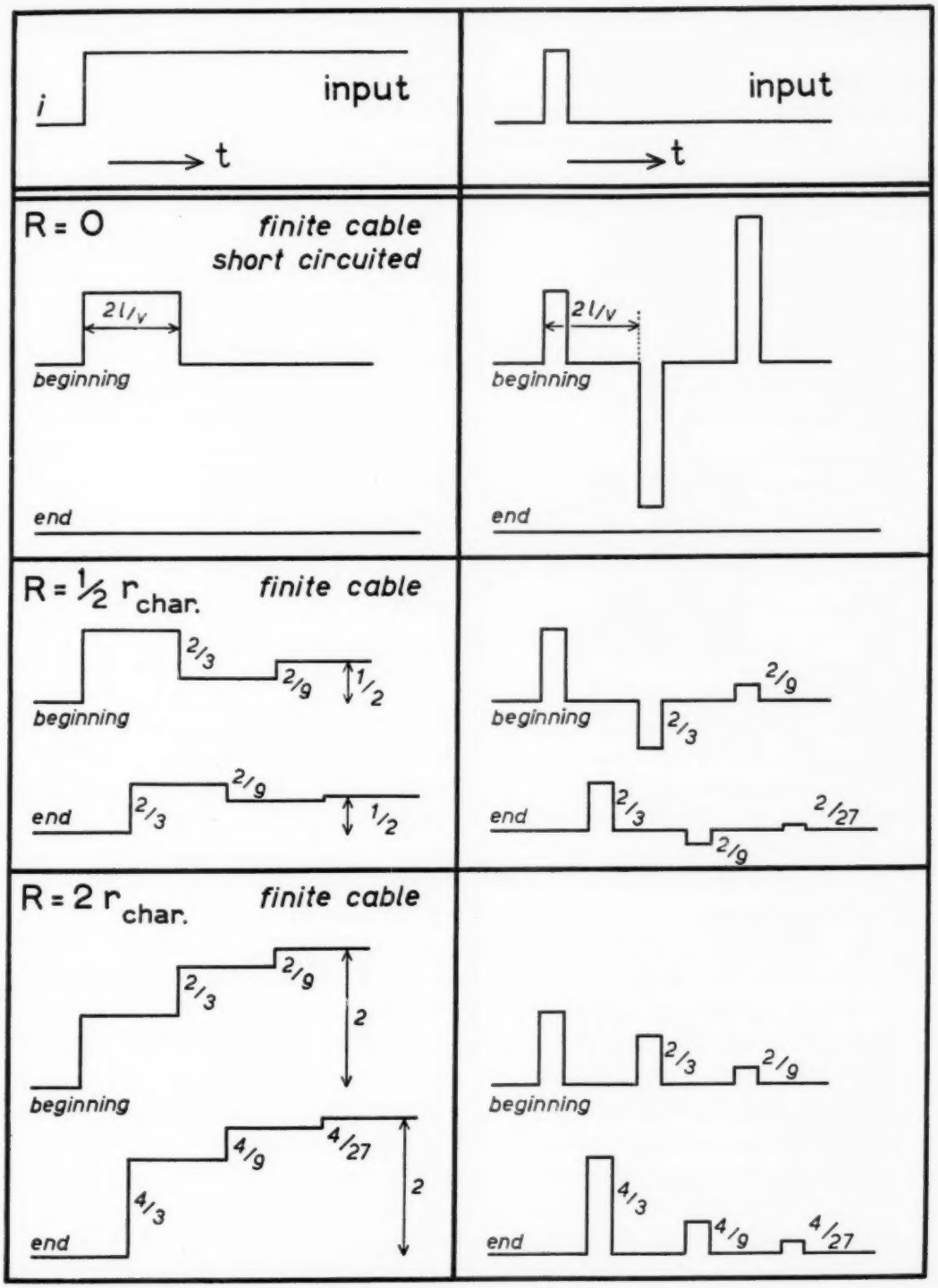


Fig. 2.—Waveforms at the beginning and the end of a cable for a constant current i lasting infinitely long and for an impulse of the same current strength. For an infinite cable the resulting potential will be also a constant equal $i \cdot R_{char.}$

For an open cable the potential will also start with $i \cdot R_{char.}$ but after a time $2\ l/v$ (the time needed for the reflected wave to return to the beginning) the reflected impulse which equals the original and has the same polarity, will add with the potential $i \cdot R_{char.}$ and be doubled. This doubling occurs because we have assumed a current source at the beginning which has an equivalent resistance ∞. After each $2\ l/v$ sec. the potential will rise with $2i \cdot R_{char.}$ and of course it must rise to infinite. At the end we find an analogous function. The first step here, however, is also $2i \cdot R_{char.}$ and starts at $t = l/v$. The



same applies to a pulse of a short duration. For a cable terminated with a resistance zero the reflected wave will be opposite and after a time 2 *l/v* just cancel the original potential as can be expected; after conditions have become stationary the total resistance equals zero and no potential can be left. For an impulse alternatively a positive or negative wave will be found with the double potential at the beginning of the cable, as is already shown before.

For $R = \frac{1}{2} R_{char.}$ the final value for a current must be $\frac{1}{2}i \bullet R_{char.}$, for an impulse this must be zero. The reflections decrease each time in amplitude and alternate in potential. For $R = 2 R_{char.}$ the final value must be $2i \bullet R_{char.}$ which value is reached by adding the reflections, which have all the same polarity. The impulses decrease according to the law of reflected waves.

tube, and E_S the volume rigidity of 1 cm. of the cable. The propagation velocity in the cable is $\sqrt{1/lc}$. For the elastic tube this means a velocity of $\sqrt{\pi r^2 E_S/\rho}$, always considering the nondamped case. This velocity is independent of frequency.

A very important factor in cable theory is the characteristic impedance. It is very useful to have a good understanding of it as much for pulse phenomena as for catheter theory. About the latter some remarks are given in Part III.

If we suddenly put a constant potential at the beginning of a cable (potential step) it will propagate uniformly since the transmission velocity is independent of frequency. The total charge will increase proportionally to time, which means that a constant current is drawn by the cable. If the cable is infinitely long it acts as a pure ohmic resistance. The value of this is called the characteristic impedance. If the cable is cut and terminated by a resistor which has this characteristic value, the cable behaves as an infinite one. No reflections will occur. The characteristic impedance is easily found with the following reasoning: If we send a constant current i into a cable, then in one second it will have passed into a length of cable of $\sqrt{1/lc}$ cm. (the wave velocity). The capacity of the cable is c per centimeter. From this it follows that the capacity of this piece is $c\sqrt{1/lc} = \sqrt{c/l}$ cm. Since $Q = CV$ (Q being the charge and C the total capacity in question) and because we take the current during one second, we have the relation $Q = i$, giving $i = CV = \sqrt{c/l} \times V = V/R_{char.}$, giving $R_{char.} = \sqrt{l/c}$. We must distinguish sharply between the characteristic (wave) resistance and the pure (Poiseuille) resistance, which determines the flow when a pressure is applied and depends on the viscosity. A rubber tube and a steel one with the same radii have the same Poiseuille resistance but not the same characteristic impedance.

To get an impression of the values which we have to deal with, we make the following assumptions: $r_{aorta} = 1$ cm.; $v = 400$ cm. sec.$^{-1}$; $\rho = 1$ g cm.$^{-3}$; so from $v = \sqrt{\pi r^2 E_S/\rho} = \sqrt{\pi E_S}$, follows $E_S = 5 \times 10^4$ dyne cm.$^{-4}$. A pulse pressure of 40 mm. Hg $= 5 \times 10^4$ dyne cm.$^{-2}$ gives rise to an expansion of 1 cm.^{3} per centimeter length, corresponding with an increase in diameter of 3 mm. This increase and the stroke volume derived from the assumed values quoted (60 ml. at a length of the aorta of 60 cm.) do not differ too much from the real values. The characteristic resistance is then $\sqrt{\rho E_S/\pi r^2} \sim 200$ dyne sec. cm.$^{-5}$. This characteristic resistance is independent of the length of the tube.

If the cable or tube is not terminated by its characteristic impedance, reflections will occur following the formula*: $V_R = (R - R_{char.})/(R + R_{char.})$ where R is the resistance the cable is connected to. If $R \gg R_{char.}$ $V_R = V$ and there is nearly a doubling of the pressure at the end. If there were no damping and the nearly doubled pressure were transmitted into a new (small) artery, large pressures could occur. When $R = 0$ a pressure pulse of a reversed sign is sent back. Some samples are shown in Fig. 2. In the nondamped case pressure and volume are only transmitted from one artery into another during the time the

*See appendix.

impulse is present at the junction of these arteries. As a rule the transmitted pressure is not equal to the pressure originally present in the first artery but equals the pressure as it occurs at the junction influenced by the reflection.

Hardung[4] makes an approximation of the various resistances considering anatomic facts. From this, he concludes that an appreciable reflection will seldom occur.

Hamilton[7] shows a recording in which the top of a femoral pressure curve is taken away by injection of Adrenalin. One could suppose that peripheral resistance may become equal to the characteristic impedance of the artery concerned so that no reflections occur any more. The injection of Adrenalin, however, gives rise to very complicated reactions. This is the reason why such

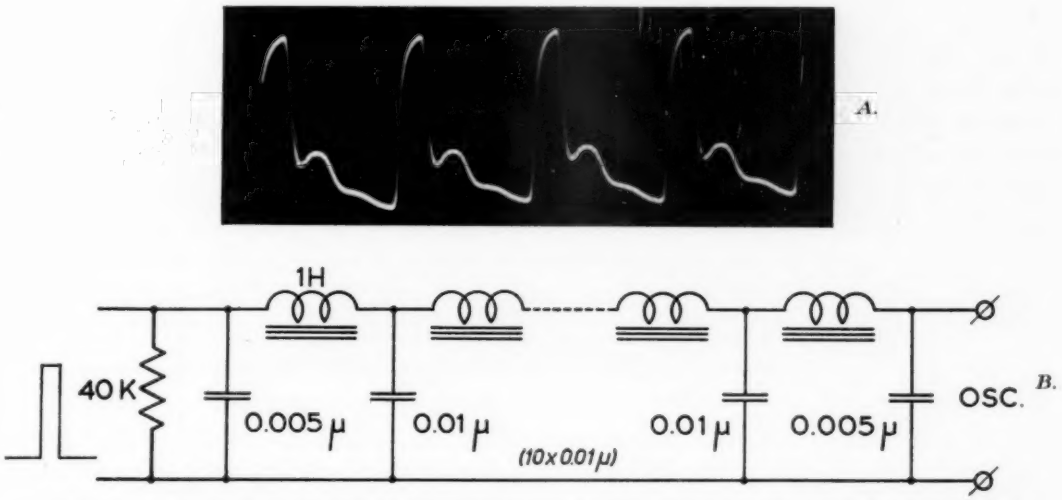


Fig. 3.—*A*, Recording of electrical impulse at the end of a delay line which simulates an electrical cable. It has a great likeness to the well-known course at the femoral side of the aorta. *B*, Circuit; a current impulse is sent into a simulated electrical cable with $R = \sim$, t = 2 millisec., f = 100 cycles. Oscillogram is taken at the end.

experiments cannot be considered decisive. One feels strongly inclined, however, to be in favor of the assumption of reflections without being certain for lack of conclusive experimental work in the field. But it is remarkable that the femoral pulse, for instance, can be so well simulated by an electrical model with a noncontinuous delay line in which reflection occurs, as can be seen in Fig. 3,*A* and *B*. The fact that here, just as in the case of the arteries, edges are rounded off results from the attenuation of high frequencies, caused by the damping which is always present.

B. Complications.—In order to prevent misunderstandings it is emphasized that the hydrodynamic pressure of blood under normal and stationary conditions is rather low. Even with velocities as high as 100 cm. sec.$^{-1}$, $\frac{1}{2}\ \rho v^2$ (kinetic energy) is equivalent to a pressure of only 4 mm. Hg. Another case occurs when a tube is closed abruptly. In that case we must take into account the kinetic

energy of all the blood moving on its way and very high pressures may be reached limited only by the elasticity. An effect like this could play a role in shaping the incisura. The negative part of the incisura, however, is a real negative pressure impulse resulting from the rather steep fall of pressure in the left ventricle and the negative pressure impulse following from this *before* the valves are closed. If a small positive wave is present after the dip, it seems that such a wave could be caused by the closure of the valves, which stops abruptly any appreciable flow: this is sometimes called the "water hammer" effect. The pressure brought about by it cannot be large, as it cannot be expected that much blood can flow back during the short time the pressure in the left ventricle is lower than in the aorta, owing to the finite transmission time of a pressure pulse in the aorta.

The aorta is sometimes regarded as an organ pipe, exhibiting a standing wave.[8,9] This is not admissible even if we accept the possibility of reflections as we do. It is clear that only recurrent excitation can result in a standing wave. In the case of the circulatory system where, evidently, damping is high, since reflections (if they occur) are damped out before a new stroke begins, we must consider the heart beats as a series of singly occurring events. Therefore Fourier analysis also is not an indicated method, and this is particularly true because there is no relation between the frequency of the recurrent heart beat and the complex of frequencies which constitute the pulse wave.

In the case of the aorta and the arterial system, corrections are needed when damping is included. If there is no damping the transmitted pressure impulse does not leave a trace. In a damped system, a continuous pressure is left after the passage of the impulse (as is shown by electrical cable theory) and this pressure gives rise to a stationary flow in the periphery.

It is also important to consider the damping in relation to energy. A pressure impulse lasting a second in an elastic tube has an energy of $P^2/R_{char.}$ (compare $V \times i$ in the electric case $= V^2/R_{char.}$); the potential energy in it is $P^2/2E$ ($\frac{1}{2} CV^2$) per centimeter length. During the second of its duration the impulse passes into a length of $\sqrt{1/lc}$ in the electrical case and of $\sqrt{\pi r^2 E/\rho}$ in the mechanical case. So we find the potential energy per second $P^2/2E \times V_w = P^2/2E \times \sqrt{\pi r^2 E/\rho} = P^2/2 \sqrt{\pi r^2/\rho E}$ (v_w = wave velocity in the mechanical case). The characteristic resistance is $\sqrt{\rho E/\pi r^2}$, and we see that the potential energy equals $P^2/2R_{char.}$ as one would expect. After the systole the total energy of the pulse wave is double its potential energy. After some tenths of a second the wave is damped out and the potential energy is the only energy present. If the wave expands throughout the aorta during systole and if the peripheral resistance were infinitely high, only reflections and no flow could occur, and after conditions had become stationary half of the transmitted energy would have been lost through the damping of the arteries. After the first time the impulse has reached a connection of arteries, however, the above-mentioned continuous pressure caused by the damping entertains a stationary flow, and also pressure is transmitted dynamically. This improves the efficiency of the system, perhaps very roughly estimated by a factor $\frac{1}{2}$. The loss of energy of the pulse wave due to damping would be $\frac{1}{4}$ in that case. This depends of course on the physiologic conditions of the system and only a detailed analysis will give reliable data.

PART III. CATHETER REFLECTIONS

As is widely known the dynamic measurement of blood pressure at the end of a catheter meets with many difficulties. Bad response of higher frequencies and reflections of many kinds may occur and distort the picture seriously. A very thorough theoretical and experimental investigation by Hansen[10] suggests methods to prevent friction losses by the use of a very rigid manometer and to obviate resonance distortion by the use of damping needles. When measuring at the end of a catheter the greatest difficulties are the catheter reflections. The catheter normally is terminated with a manometer which is rather rigid. This catheter resembles an artery, as it is an elastic tube in which a pressure wave travels and may be reflected. The damping in a catheter is much lower than in an artery,

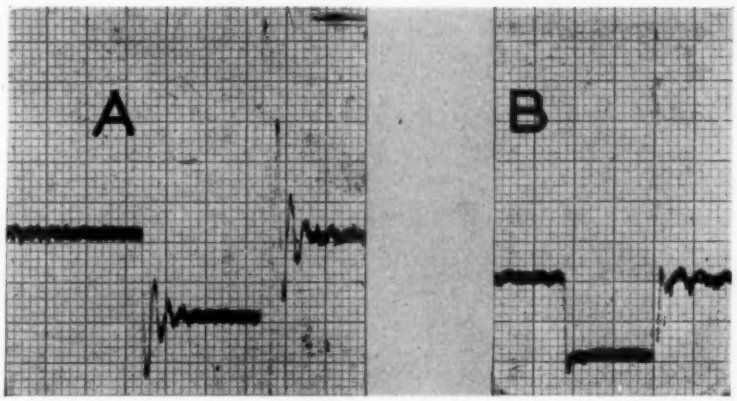
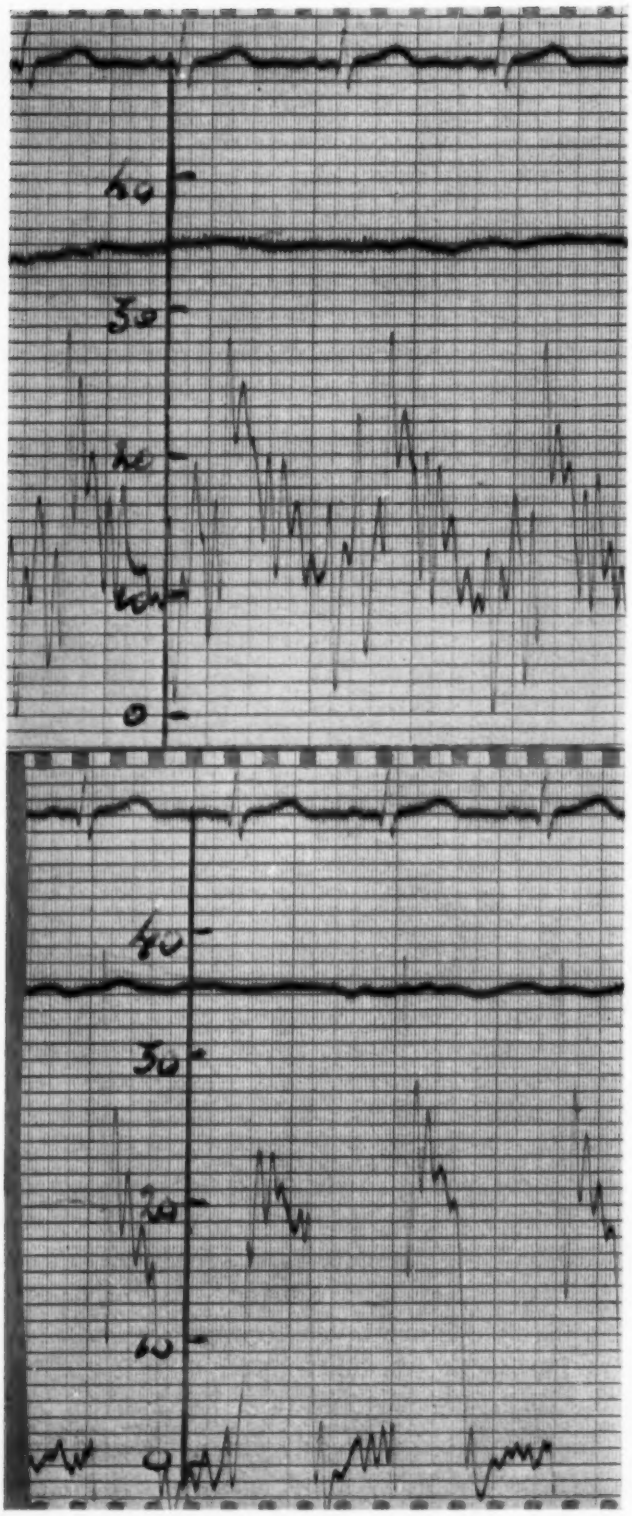


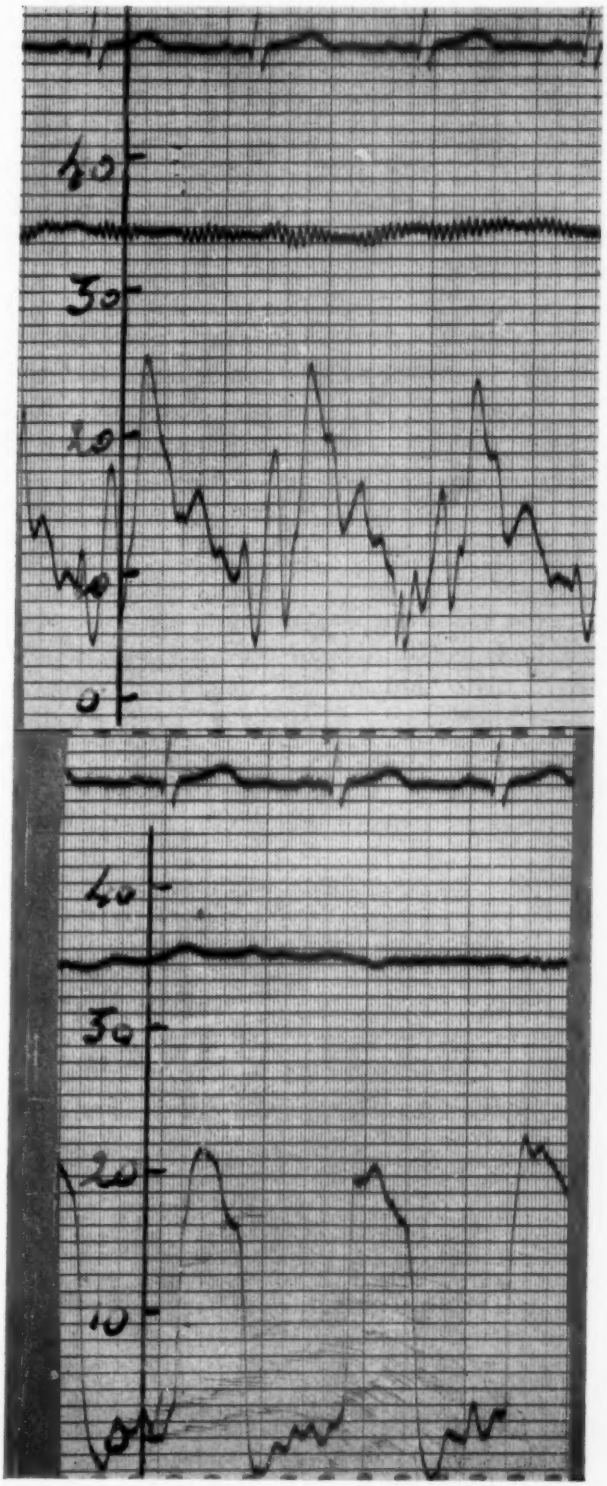
Fig. 4.—A pressure step is made by opening a valve and allowing water under hydrostatic pressure to flow into free space. By stopping the flow one gets a step function plus an impulse function. *A* is without any parallel damping, *B* with a needle parallel to the catheter and coming out into open air. With the catheterization one should connect the needle to a pressure source somewhat higher than the mean blood pressure, preventing the entrance of blood in catheter and needle.

so these reflections play an important role in the registration as they obscure the real shape of the tracing. The solution of the problem is obvious if only the simple treatment of transmission of pressure waves is wholly understood. We have to terminate the elastic catheter with its characteristic impedance. If now this characteristic impedance is high compared with the Poiseuille resistance of the whole catheter, the waves will arrive undistorted at the end of the catheter. The amplitude, however, will be decreased depending upon the ratio of the Poiseuille resistance and the characteristic resistance. In different cases, the wave impedance of a catheter will be different. We propose, therefore, the use of a needle with a variable lumen in the form of a valve. This needle must be used parallel with the manometer and run out into free space. The results of model experiments are given in Fig. 4, with real catheterizations in Fig. 5. From these figures, it is clear that these results are not caused by cutting off higher frequencies. When, on the other hand, a series damping is introduced, the reflections may be eliminated but only at the cost of the extinction of higher frequencies. As a result this method strongly distorts the recording.



A.

Fig. 5.—Pressure registration with a catheter No. 7: *I*, Artery pulmonalis dextra; *II*, Right ventricle. *A* without and *B* with a parallel "damping" needle.



B.

Fig. 5.—Cont'd. *B (For legend see opposite page).*

When we take data from Hansen concerning catheters we find the following values:

$$v_w = 20{,}000 \text{ cm. sec.}^{-1},\ r = 6.10^{-2} \text{ cm.},\ L_e = 100 \text{ cm.}$$

For the inductance per centimeter we find $l = \rho/\pi r^2 = 10^{-2}$ g cm.$^{-5}$. Now $R_{char.} = v \times l$ or $R_{char.} = 2 \times 10^6$ dyne sec. cm.$^{-5}$. The total Poiseuille resistance of the catheter (filled with water) is $8\eta L_e/\pi r^4 = 2 \times 10^5$ dyne sec. cm.$^{-5}$. If terminated by its characteristic resistance a 10 per cent decrease in amplitude can be expected in this case.

As Ranke[11] pointed out, at higher frequencies the flow pattern will differ from those used in Poiseuille's law. This will result in some distortion. Apart from this distortion there is always a distortion as a result of the nonideal elastic properties of the catheter itself. The results of our model experiments show these distortions as a smoothing of the pulse shape. However, the reflections are important already in a much lower frequency range and can be eliminated with the proposed procedure. Ranke proposes the use of a "nearly infinitely" long catheter as terminating resistance. This is theoretically the best one can do, but does not seem very practical.

Hansen proposes the use of a series damping, but since his manometer is very stiff this damping can only partly prevent reflection with catheters with a great volume rigidity and a high "inductance" (small catheters) in the frequency regions where this is of importance. If larger catheters are used the system can not dissipate the energy of the traveling wave when the manometric impedance (capacitive impedance) is high compared with the characteristic impedance. The only thing that happens then is cutting off high frequencies.

Many thanks are due to Dr. Rodrigo and Professor Snellen from the cardiological department at the University of Leyden for their help in preparing this paper, for their enthusiasm in establishing the usefulness of the damping method, and the demonstrative recordings shown in the figures. As usual the critical interest of Dr. H. den Hartog and Dr. F. A. Muller from the Physical Laboratory of the University of Amsterdam was of great value at many important points.

REFERENCES

1. van der Tweel, L. H.: Dynamometric Determination of Blood Pressure, Nederl. tijdschr. geneesk. **96**:1459, 1952.
2. Wiggers, C. J.: Circulatory Dynamics: Physiologic Studies, New York, 1952, Grune & Stratton, Inc.
3. Hallock, P., and Benson, I. C.: Studies on Elastic Properties of Human Isolated Aorta, J. Clin. Invest. **16**:595, 1937; ref. Med. Physics **1**: 1951.
4. Hardung, V.: Zur mathematischen Behandlung der Dämpfung und Reflexion der Pulswellen, Arch. Kreislaufforsch. **18**:167, 1952.
5. Hamilton, W. F.: Med. Physics **1**:7, 1951.
6. Peterson, L. H.: Circulation Research **2**:127, 1954.
7. King, E. L.: J. Appl. Physics 595, 1947.
8. Hamilton, W. F., and Dow, P.: Experimental Study of Standing Waves in Pulse Propagated Through the Aorta, Am. J. Physiol. **125**:48, 1939.

8a. Dow, P., and Hamilton, W. F.: Experimental Study of Velocity of Pulse Wave Propagated Through the Aorta, Am. J. Physiol. **125**:60, 1939.

9. Alexander, W. F., et al.: Circulation Research **1**:16, 1953.
10. Hansen, A. T.: Thesis, Copenhagen, 1949, Teknisk Forlag.
11. Ranke, O. F.: Registrierung laufender Wellen als Registrierprinzip, Arch. Kreislaufforsch. **18**:99, 1952.

APPENDIX

FORMULAE

Electric Cable.—For an electric cable the following formulae apply:

$$1.\quad \frac{\delta V}{\delta x} = -\, l\, \frac{\delta i}{\delta t}$$

$$2.\quad \frac{\delta V}{\delta t} = -\, \frac{1}{c}\, \frac{\delta i}{\delta x}$$

If we take the mechanical formulae for the liquid in a tube, we get:
(a) $\pi r^2 \cdot \delta P/\delta x$: the force resulting from the pressure gradient, and (b) $\pi r^2 \rho \cdot \delta v/\delta t$: the product of mass and acceleration. Note that v is the real velocity of a liquid particle, *not* that of the wave (v_w). The analogue of the electric current is the quantity of liquid flowing in a second $f = \pi r^2 v$. The sum of a and b must be zero, so $\delta P/\delta x = -\, \rho/\pi r^2 \cdot \delta f/\delta t$ and the analogue of 2 gives: $\delta P/\delta t = -\, E \cdot \delta f/\delta x$. The analogue of the inductance is $\rho/\pi r^2$. Also in manometer theory a term occurs that is an analogue of inductance, and perhaps one should expect that a larger mass (larger radius) would mean a larger inertia. But we must always use the total force, which is proportional to r^2 as well. When we take further into account that the displacement of a fixed quantity of liquid is inversely proportional to r^2, we can readily understand the given formula.

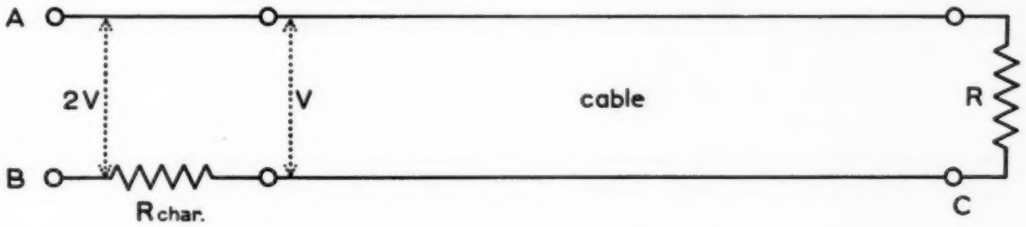


Fig. 6.—Circuit for the computation of the amplitude of the reflected wave as a function of the terminating resistance R and $R_{char.}$

Reflected Waves.—The formula for the reflected wave $V_R = (R - R_{char.})/(R + R_{char.})\ V$ can be obtained by the following reasoning (Fig. 6).

A potential step 2 V is applied between A and B, connected with a resistor $R_{char.}$ to the cable. Therefore a potential step equal to V is transmitted through the cable. At point C a part of this, say V_R, is reflected. When this comes to the resistor $R_{char.}$ it is absorbed (according to the definition of the characteristic impedance). At point C results $V + V_R$. But since the only reflection that could occur has disappeared the situation has become stationary, and we can apply Ohm's law. The pure resistance of the cable is supposed to be zero; therefore we find

$$V + V_R = R/(R_{char.} + R) \times 2\ V \text{ or } V_R = (R - R_{char.})/(R + R_{char.}) \times V \text{ (Fig. 6).}$$

Also, of course, the energy and the transmitted charge (volume) have to be continuous, which follows from the formulae in the following way. The energy of an elastic wave is given by $V^2/R_{char.}$ For the original, the transmitted and the reflected waves apply

$$V^2/R_{char.} = V_R^2/R_{char.} + (V + V_R)^2/R$$

since the transmitted pressure is just $V + V_R$. When we substitute $V_R = (R - R_{char.})/(R + R_{char.}) \times V$, we easily see that the formula is correct. The transmitted and reflected pulses have the same duration as the original pulse, so we may substitute charge with current, and then this continuity also is easily demonstrated.

RELATIONSHIPS BETWEEN ELECTRICAL AND MECHANICAL EVENTS IN ATRIAL FIBRILLATION: A STUDY OF DIRECT ARTERIAL PRESSURE TRACINGS

S. Z. Rosenberg, M.D., M. Eliakim, M.D., and K. Braun, M.D.

Jerusalem, Israel

ANALYSIS of the relationship between the electrical and mechanical events in atrial fibrillation may lead to better understanding of the hemodynamics of this cardiac arrhythmia. Little is known about the interval between the onset of the electrical systole and mechanical systole (electrical-mechanical latent period) in atrial fibrillation, and its relation to other time intervals of the cardiac cycle and to systemic blood pressure. Buchbinder and Sugarman[1] found by direct arterial pressure recordings that the electrical-mechanical latent period varied in atrial fibrillation and was inversely related to the length of the previous cycle. On the other hand, Coblentz and associates[2] observed no constant relationship between cycle length and variations in the electrical-mechanical latent period in records obtained similarly.

The purpose of this study was to determine the relation of the electrical-mechanical latent period to other time intervals of the cardiac cycle and to the blood pressure in atrial fibrillation.

MATERIAL AND METHOD

Ten patients suffering from inactive rheumatic valvular heart disease were selected for this study. All had chronic atrial fibrillation with ventricular rates varying between 70 and 138 beats per minute; five had signs of congestive failure. The control group consisted of five patients with no evidence of cardiovascular disease; in all of them sinus arrhythmia was present.

Direct brachial arterial pressure records and electrocardiograms were obtained simultaneously by means of an electromanometer* and a direct two-channel recording apparatus.* Paper speed was 25 mm. per second permitting time intervals to be estimated within 0.01 sec. The time necessary for the transmission of the mechanical impulse from the arterial needle to the recording system was 0.01 sec., and was not taken into consideration in the reported measurements.

The following measurements in each record were made in 50 consecutive beats: (1) the electrical-mechanical latent period (EMLP) i.e., the interval

---

From the Cardiovascular Laboratory and the Department of Medicine, Division 'B,' Rothschild Hadassah University Hospital, Jerusalem, Israel.

This study was supported by the Philip D. Lown Fund.

Received for publication March 28, 1956.

*Sanborn.

between the beginning of the QRS complex and the upstroke of the arterial pressure of the corresponding beat; (2) cycle length (Q-Q interval); (3) systolic pressure; (4) initial pressure (end-diastolic pressure of the preceding beat); (5) pulse pressure (computed from the initial and systolic pressures); (6) mechanical diastole (from the lowest point of the dicrotic notch to the onset of the following upstroke); (7) mechanical systole (from the beginning of the upstroke to the lowest point of the dicrotic notch). The time intervals were determined in hundredths of a second and the pressures in millimeters of mercury.

We have investigated the relation of the EMLP to (a) the preceding cycle length; (b) preceding mechanical diastole; (c) initial pressure; (d) systolic pressure; (e) pulse pressure; and (f) the mechanical systole. Furthermore, the relation between pulse pressure and the preceding cycle length was studied.

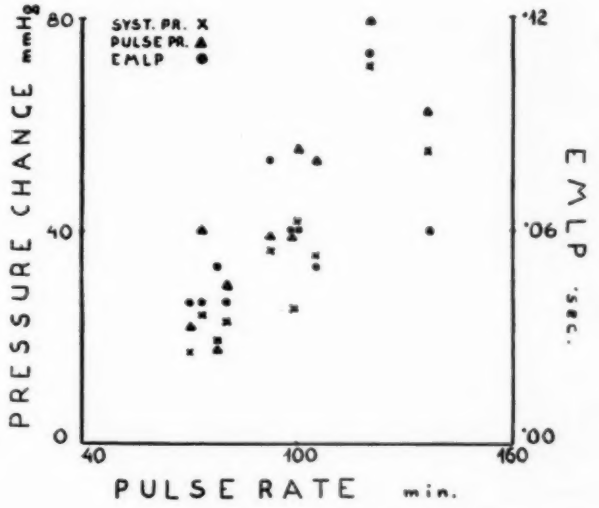


Fig. 1.—Relation between pulse rate and maximal change of EMLP, systolic pressure, and pulse pressure in ten cases of atrial fibrillation.

RESULTS

Tracings of patients with rapid, completely irregular ventricular rates showed a different pattern from those with slow and less irregular ventricular rates. The range of variations of the different time intervals and pressures in all cases of atrial fibrillation is presented in Table I. The maximal change of the EMLP, the pulse pressure, and the systolic pressure in each case was related to the ventricular rate (Fig. 1). It may be seen from Table I and Fig. 1 that an increase of ventricular rate was usually accompanied by increased variations in the different time intervals and pressures measured. However, the range of variations appeared to be also dependent on the irregularity of the ventricular rhythm and not only on the ventricular rate.

TABLE I. RANGE OF VARIATIONS OF DIFFERENT TIME INTERVALS AND PRESSURES IN TEN CASES OF ATRIAL FIBRILLATION

	VENTRICULAR RATE (BEAT/MIN.)	EMLP (SEC.)	CYCLE LENGTH (SEC.)	SYSTOLIC PRESSURE (MM. HG.)	INITIAL PRESSURE (MM. HG.)	PULSE PRESSURE (MM. HG.)	MECHANICAL SYSTOLE (SEC.)	MECHANICAL DIASTOLE (SEC.)
1. C.Z. ♂	70	0.19–0.23 (0.04)	0.71–121 (0.50)	107–124 (17)	62–85 (23)	30–52 (22)	0.21–0.24 (0.03)	0.5 –1.00 (0.5)
2. R.K. ♀	73	0.16–0.20 (0.04)	0.57–1.25 (0.68)	132–156 (24)	58–84 (26)	52–92 (40)	0.24–0.32 (0.08)	0.34–0.94 (0.60)
3. Ð.P. ♀	78	0.18–0.23 (0.05)	0.60–1.00 (0.40)	104–122 (18)	69–83 (14)	24–42 (18)	0.22–0.30 (0.08)	0.38–0.88 (0.50)
4. I.J. ♀**	80	0.12–0.16 (0.04)	0.51–0.95 (0.44)	102–125 (23)	32–55 (23)	55–85 (30)	0.20–0.26 (0.06)	0.30–0.72 (0.42)
5. B.A. ♂	92	0.16–0.24 (0.08)	0.50–0.96 (0.46)	65–101 (36)	45–62 (17)	8–47 (39)	0.20–0.24 (0.04)	0.28–0.75 (0.47)
6. M.J. ♂	99	0.12–0.18 (0.06)	0.44–0.94 (0.50)	95–120 (25)	55–70 (15)	25–65 (40)	0.20–0.28 (0.08)	0.22–0.70 (0.48)
7. B.Z. ♂	100	0.17–0.23 (0.06)	0.48–0.80 (0.32)	90–130 (40)	65–82 (17)	10–65 (55)	0.16–0.24 (0.08)	0.20–0.60 (0.40)
8. I.H. ♀	105	0.12–0.17 (0.05)	0.37–0.76 (0.39)	85–120 (35)	42–63 (21)	22–75 (53)	0.16–0.30 (0.14)	0.16–0.76 (0.60)
9. F.L. ♂*	120	0.12–0.23 (0.11)	0.36–0.96 (0.60)	107–178 (71)	82–122 (40)	1–80 (79)	0.10–0.26 (0.16)	0.24–0.72 (0.48)
10. S.D. ♂	138	0.15–0.21 (0.06)	0.31–0.66 (0.35)	80–135 (55)	62–87 (25)	1–64 (63)	0.13–0.22 (0.09)	0.15–0.42 (0.27)

( ) = difference between the two extreme values.
*Case 1.
**Case 2.

The data of one case with rapid ventricular rate (Case 1) and another case with slow ventricular rate (Case 2) were studied in detail and compared with the data of one of the control cases (Case 3) with sinus arrhythmia. The results obtained in the four remaining controls were almost identical with those of Case 3.

The electrical-mechanical latent period in Case 1 ranged between 0.12 and 0.23 sec., in Cases 2 and 3 between 0.12 and 0.16 sec.

Relationship Between the EMLP and the Length of the Preceding Cycle.—In atrial fibrillation with rapid ventricular rate (Case 1) the cycle length varied widely, from 0.36 to 0.96 sec. (Fig. 2). There was a significant inverse correlation between the EMLP and the length of the preceding cycle, the regression coefficient, r, being -0.69, $p < 0.001$. In the case of atrial fibrillation with slow ventricular rate (Case 2), the cycle length varied less (0.51 to 0.95 sec.), and no correlation with the EMLP was found (r -0.08, p 0.58). In the case

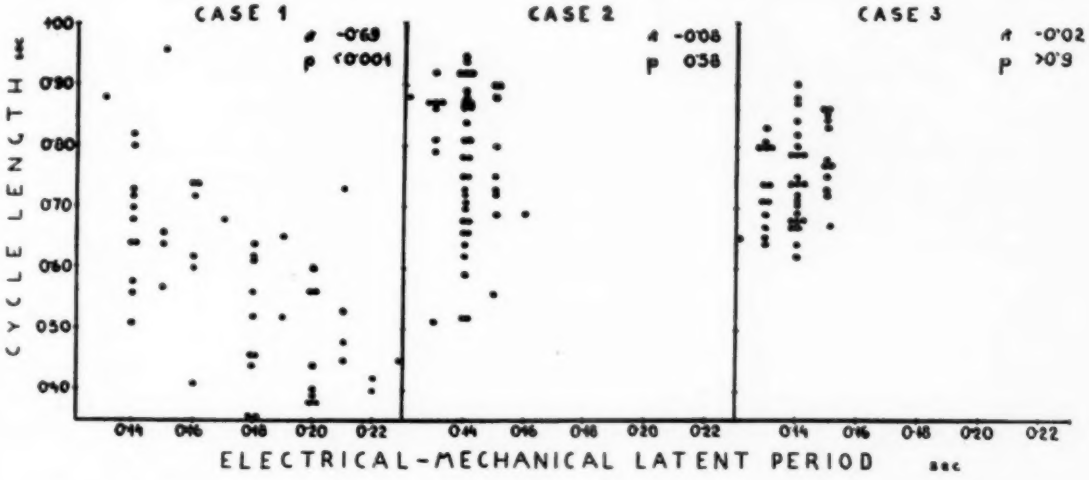


Fig. 2.—Relation between EMLP and preceding cycle length in atrial fibrillation with rapid ventricular rate (Case 1), in atrial fibrillation with slow ventricular rate (Case 2), and in a case of sinus arrhythmia (Case 3).

with sinus arrhythmia (Case 3) there was even less variation in the cycle length (0.62 to 0.90 sec.) and here again no correlation with the EMLP was noted (r -0.02, $p > 0.9$). The variability in the cycle length in Case 3 was due to respiratory arrhythmia.

Relationship Between the EMLP and the Duration of the Preceding Mechanical Diastole.—In Case 1 the length of the diastole varied between 0.24 and 0.72 sec. Half of the beats had a diastole shorter than 0.40 sec. (Fig. 3). There was a significant inverse correlation between the EMLP and the duration of the preceding mechanical diastole (r -0.73, $p < 0.001$). In Case 2 the diastole varied between 0.30 and 0.72 sec., but it was shorter than 0.40 sec. in only 5 beats. There was no correlation between EMLP and the duration of the preceding mechanical diastole (r -0.17, p 0.25). In Case 3 the mechanical diastole ranged between 0.46 and 0.75 sec. There was no correlation between the EMLP and the preceding mechanical diastole (r 0.31, p 0.03).

Relationship Between the EMLP and the Initial Pressure.—In Case 1 the initial pressure varied between 82 and 122 mm. Hg. There was a fairly good direct correlation between the EMLP and the height of the initial pressure (r 0.65, p < 0.001) (Fig. 4). In Case 2 the variations in the initial pressure

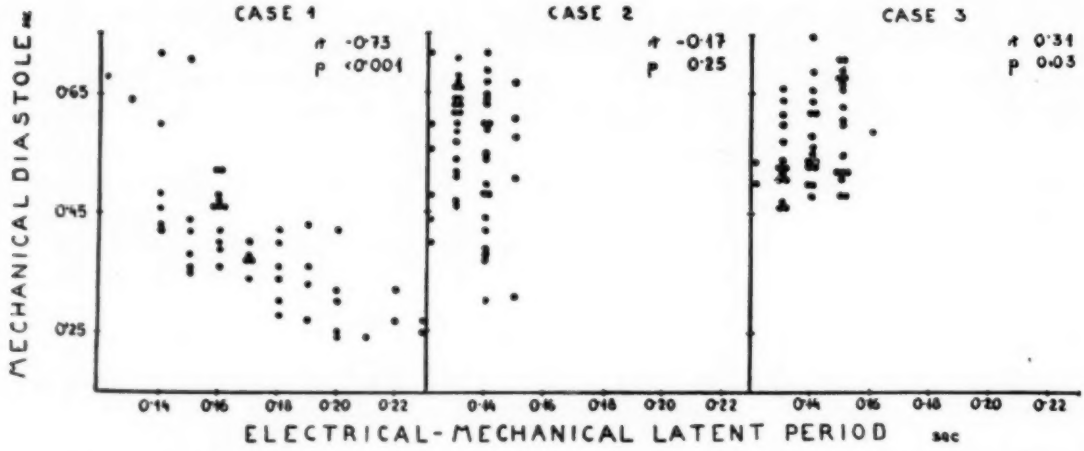


Fig. 3.—Relation between EMLP and duration of preceding mechanical diastole in atrial fibrillation with rapid ventricular rate (Case 1), in atrial fibrillation with slow ventricular rate (Case 2), and in a case of sinus arrhythmia (Case 3).

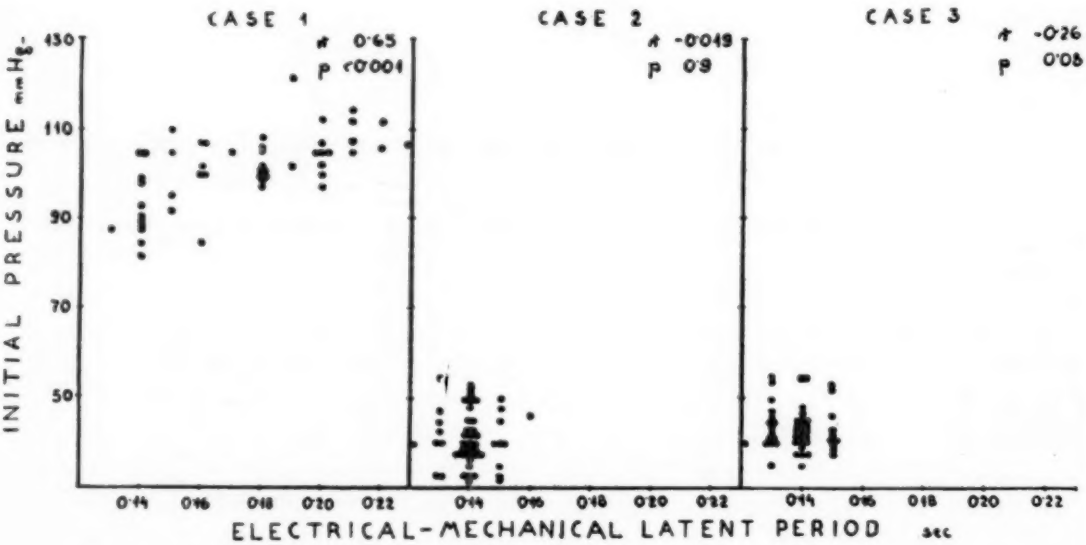


Fig. 4.—Relation between EMLP and initial pressure in atrial fibrillation with rapid ventricular rate (Case 1), in atrial fibrillation with slow ventricular rate (Case 2), and in a case of sinus arrhythmia (Case 3).

were less pronounced, ranging between 32 and 55 mm. Hg and no correlation with the EMLP was found (r −0.019, p 0.9). In Case 3 the variations of the initial pressure were similar to those in Case 2 and here again no correlation with the EMLP was found (r −0.26, p 0.08).

Relationship Between the EMLP and the Systolic Pressure.—The systolic pressure varied very widely in Case 1 (107 to 178 mm. Hg), less in Case 2 (102 to 125 mm. Hg) and even less in Case 3 (100 to 115 mm. Hg) (Fig. 5). A significant inverse correlation between the EMLP and the systolic pressure was found in Case 1 ($r -0.68$, $p < 0.001$), while no correlation existed in Cases 2 and 3 (r 0.01, $p > 0.9$, and r 0.16, p 0.27, respectively).

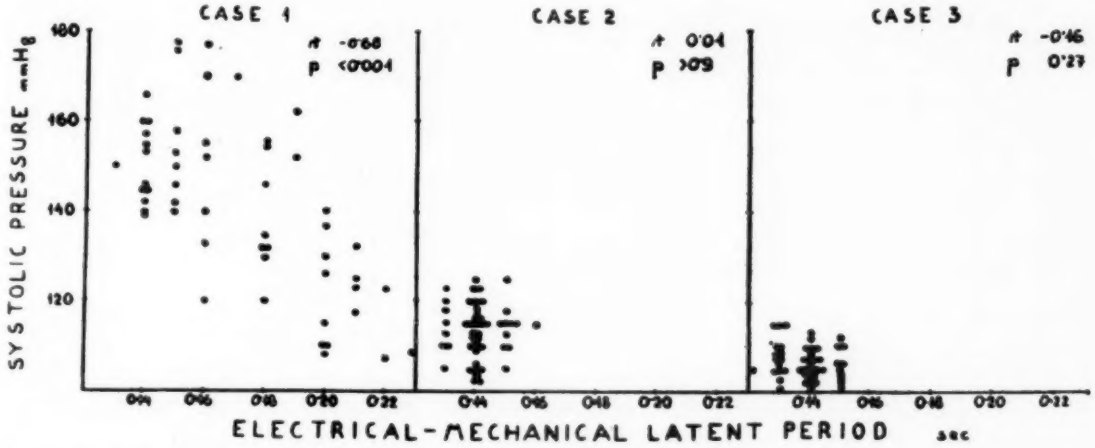


Fig. 5.—Relation between EMLP and systolic pressure in atrial fibrillation with rapid ventricular rate (Case 1), in atrial fibrillation with slow ventricular rate (Case 2), and in a case of sinus arrhythmia (Case 3).

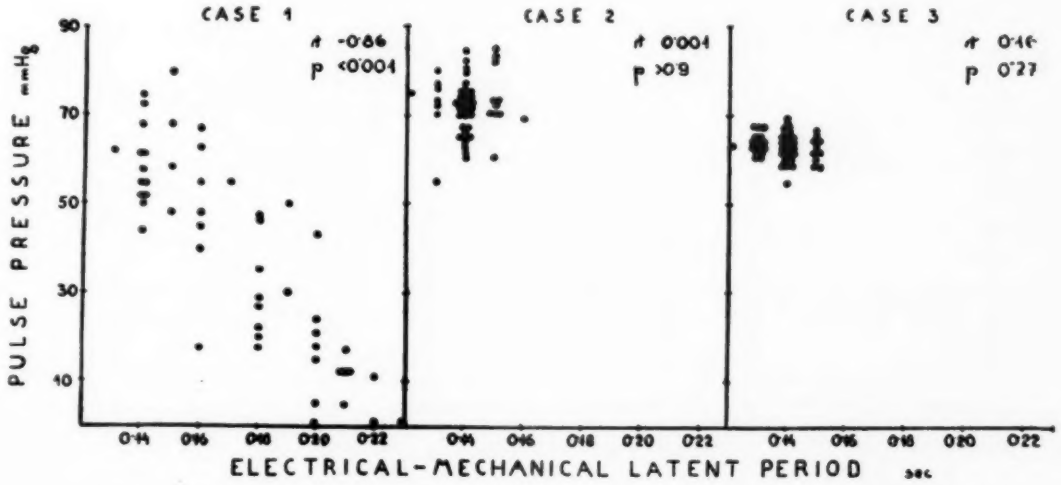


Fig. 6.—Relation between EMLP and pulse pressure in atrial fibrillation with rapid ventricular rate (Case 1), in atrial fibrillation with slow ventricular rate (Case 2), and in a case of sinus arrhythmia (Case 3).

Relationship Between the EMLP and the Pulse Pressure.—The pulse pressure showed extreme variations in Case 1 (1 to 80 mm. Hg), smaller variations in Case 2 (55 to 85 mm. Hg), and still less variations in Case 3 (55 to 69 mm. Hg) (Fig. 6). A significant inverse correlation existed between the EMLP

and the pulse pressure in Case 1 ($r -0.86$, $p < 0.001$), but no correlation was found in Case 2 (r 0.001, $p > 0.9$) and in Case 3 (r 0.16, p 0.27).

Relationship Between the EMLP and the Duration of the Mechanical Systole.—The duration of the mechanical systole ranged from 0.10 to 0.26 sec. in Case 1, 0.20 to 0.26 sec. in Case 2, and 0.15 to 0.20 sec. in Case 3. There was

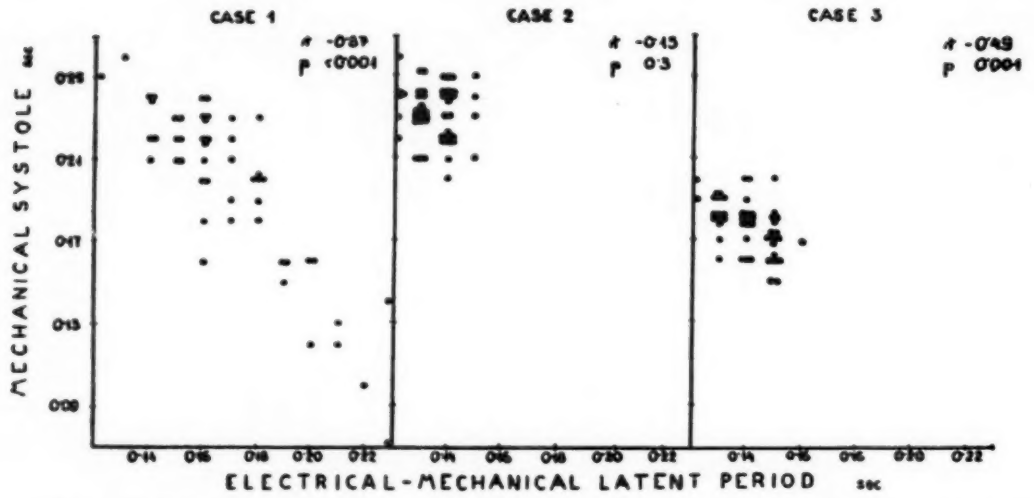


Fig. 7.—Relation between EMLP and duration of mechanical systole in atrial fibrillation with rapid ventricular rate (Case 1), in atrial fibrillation with slow ventricular rate (Case 2), and in a case of sinus arrhythmia (Case 3).

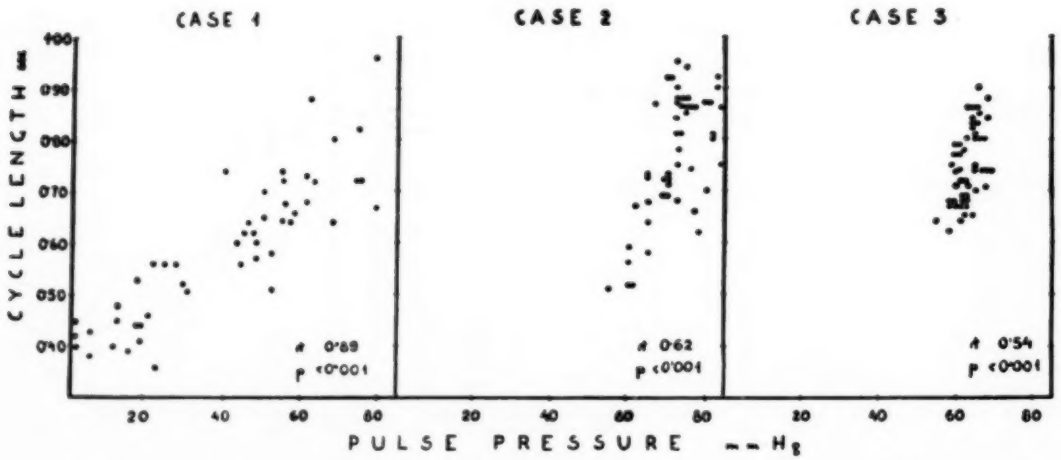


Fig. 8.—Relation between pulse pressure and length of preceding cycle in atrial fibrillation with rapid ventricular rate (Case 1), in atrial fibrillation with slow ventricular rate (Case 2), and in a case of sinus arrhythmia (Case 3).

a significant inverse correlation between the EMLP and the duration of the mechanical systole in Case 1 ($r -0.87$, $p < 0.001$), while no correlation between these factors was found in Case 2 ($r -0.15$, p 0.3) and in Case 3 ($r -0.49$, p 0.001) (Fig. 7).

Relationship Between the Pulse Pressure and the Length of the Preceding Cycle.—A remarkably good direct correlation was found in Case 1, between the pulse pressure and the length of the preceding cycle (r 0.89, $p < 0.001$). In Case 2 the correlation was less marked (r 0.62, $p < 0.001$) and it was still less in Case 3 (r 0.54, $p < 0.001$) (Fig. 8).

COMMENT

The interval between the beginning of the QRS complex and the upstroke of the arterial pressure curve is composed of four periods: the interval between the Q wave and the onset of the left ventricular isometric contraction (A), the duration of the isometric contraction (B), the time required for transmission

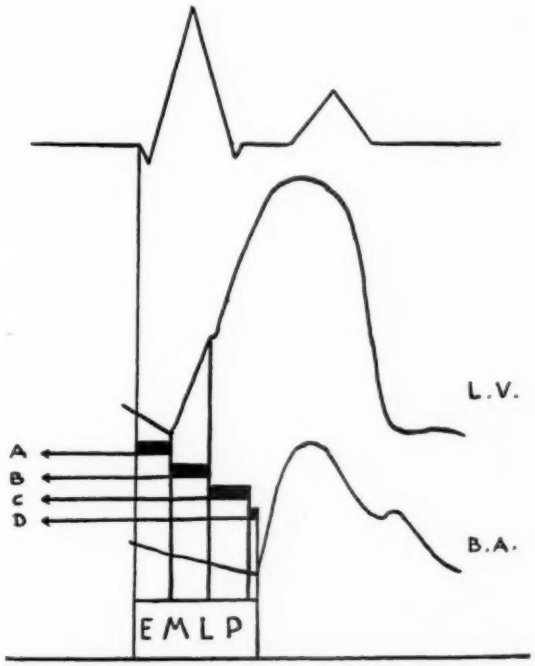


Fig. 9.—The four components of the period between the beginning of the QRS complex and the upstroke of the arterial pressure curve (EMLP). *L.V.* = left ventricle. *B.A.* = brachial artery.

of the mechanical impulse to the peripheral artery (C), and the time lag from the arterial needle to the recording system (D) (Fig. 9). The last period was found to be 0.01 sec. and was constant since the same equipment was used throughout the whole study.

The average duration of the period between the Q wave and the beginning of the left ventricular isometric contraction (A) is 0.041 sec.[3] This period for the right ventricle has been shown to vary inversely with the length of the preceding cycle in atrial fibrillation and with the degree of prematurity of ectopic beats. Normal beats following ectopic beats had a short latent period, apparently because the muscle was less refractory after a long recovery phase.[4]

It appears, therefore, that the degree of refractoriness of the myocardium influences the duration of this period.

The isometric contraction of the left ventricle (B) lasts 0.04 to 0.06 sec.[3] This time interval is influenced by the ventricular rate, by mechanical obstacles to the blood flow, by the pathway of the electrical stimulus, and by the stroke volume. In atrial fibrillation the length of the isometric contraction varies directly with the initial pressure[5] and thus inversely with the length of the previous cycle.

The time required for transmission of the pulse wave from the aortic valve to the peripheral artery (where the needle is inserted) (C) is influenced by the distensibility of the arterial wall and by the intra-arterial pressure.[6] The limb arteries are comparatively indistensible and the pulse wave velocity in them varies between 7 and 14 meters per second.[7] If the average distance from the heart to the brachial artery is assumed to be 50 cm., the time necessary for the mechanical impulse to reach the arterial needle would vary between 0.07 to 0.035 sec. There are no data available to us on the pulse wave velocity in atrial fibrillation but it probably depends on the intra-arterial pressure at a given moment.

Our findings demonstrate a tendency for inverse correlation between the EMLP and the length of the preceding cycle in atrial fibrillation with rapid, irregular ventricular rate. This was to be expected since, as mentioned above, periods A and B of the EMLP are both inversely related to the previous cycle length. Since the EMLP represents the resultant of four periods, three of which (A, B, and C) are variable and dependent on different factors, it is evident that the range of variations of EMLP is wide in the presence of rapid, irregular ventricular rate.

There is an inverse correlation between the EMLP and the duration of the mechanical systole of a beat (Fig. 7). The mechanical systole would be expected to lengthen with an increase of stroke volume, i.e., after long cardiac cycles. It seems, therefore, that both the EMLP and the mechanical systole are affected by the length of the previous cycle and, hence, the inverse correlation between the EMLP and the mechanical systole.

It has been confirmed in this study that in atrial fibrillation long cycles terminate with comparatively low diastolic pressures and are followed by beats with high systolic and large pulse pressures[1] (Fig. 10). The low initial pressure of beats following long cardiac cycles is explained by more complete emptying of the arterial tree during a long diastole. The higher systolic pressure of beats following long cardiac cycles is due to the expulsion of large amounts of blood as a result of more complete ventricular filling and the more efficient ventricular contraction after a long recovery period. However, the cycle length and particularly the duration of the mechanical diastole are not the only factors determining the systolic and the pulse pressures, since different systolic and pulse pressures may follow cycles of equal lengths. Disturbance in the synergic contraction of the ventricular muscle fibers may explain the differences in pressures in the pulse tracing after cycles of equal length.[1,5] It is reasonable to assume that the mechanical efficiency of a beat is determined not only by the

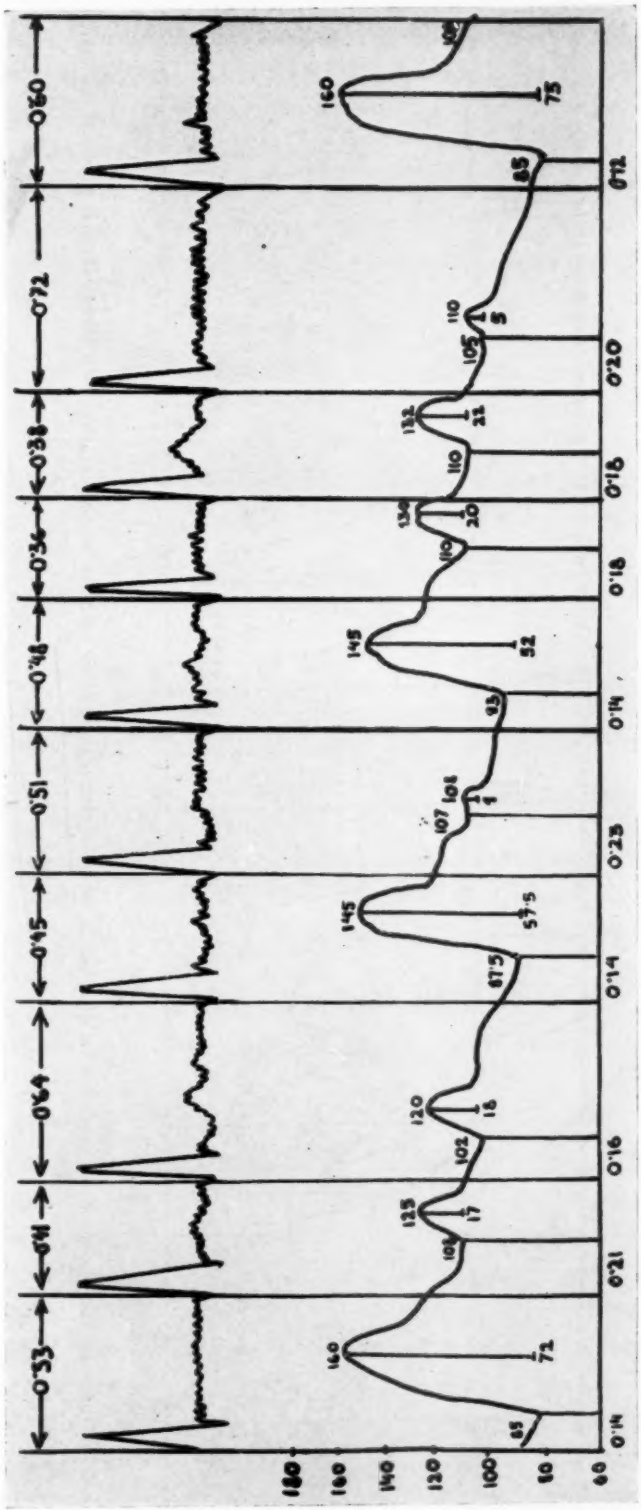


Fig. 10.—Time intervals and pressures in a case of atrial fibrillation with rapid ventricular rate. Schematic presentation of a direct arterial pressure tracing.

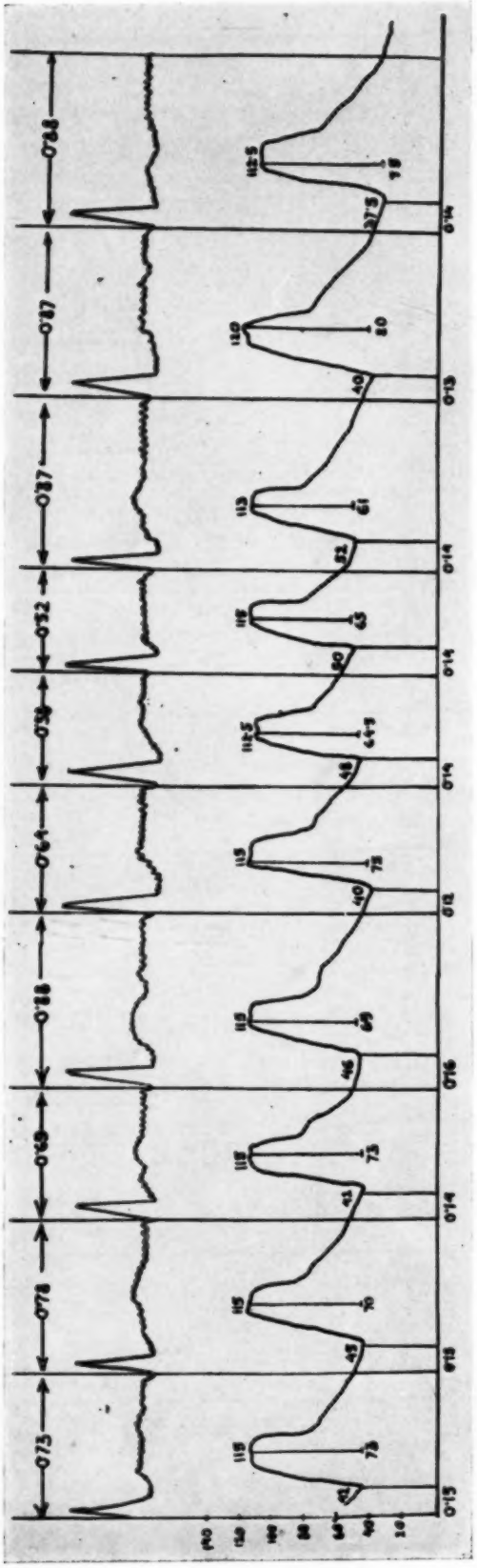


Fig. 11.—Time intervals and pressures in a case of atrial fibrillation with slow ventricular rate. Schematic presentation of a direct arterial pressure tracing.

immediate preceding beat but also by a number of earlier beats. The efficiency of the ventricular contraction diminishes progressively in a series of beats with equal but short diastoles.

While even superficial inspection of the arterial pressure tracing of the patient with rapid ventricular rate reveals great differences in cycle length and pressures, one is impressed by the gross regularity of the pulse and constance of pressures in the case with slow ventricular rate. In contrast to Case 1 in which the marked changes in cycle length and the rapid pulse rate led to many inefficient beats, as expressed by extremely small pulse pressures (Table I, Fig. 10), in Case 2 the cycle length varied less and the shortest cycle was 0.51 sec. Since the diastole of this cycle length is apparently sufficient for complete or nearly complete ventricular filling and permits satisfactory ventricular recovery, the pressures were not markedly affected by the changing cycle length. A representative illustration is given in Fig. 11 where the systolic pressures showed little change after one of the shortest and one of the longest cycles (0.52 and 0.87 sec.). The remarkably small variations of the EMLP in Case 2 are apparently the result of the slow and more regular pulse rate. It is evident from the above that the slow pulse affects favorably the hemodynamic efficiency of the ventricular contraction.

The variations of the different time intervals and pressures in the patient with sinus arrhythmia (Case 3) resembled those in Case 2; however, they were less pronounced.

It may be concluded that, in atrial fibrillation with rapid, grossly irregular ventricular rate, pronounced changes in EMLP, cycle length, mechanical systole and diastole, and in pressures take place. These changes certainly indicate reduced hemodynamic efficiency of the circulation. On the other hand, atrial fibrillation with slower, more regular ventricular rate causes changes which are almost equal to those induced by the physiologic sinus arrhythmia. The data presented above furnish additional proof for the value of slowing the pulse rate in atrial fibrillation.

SUMMARY

Direct arterial pressure tracings of ten patients with atrial fibrillation and of five normal subjects with sinus arrhythmia were analyzed. In patients with atrial fibrillation with rapid, irregular ventricular rate the period between the Q wave and the upstroke of the arterial pressure curve was inversely related to the cycle length and the mechanical diastole of the preceding beat, to the systolic and pulse pressures, and to the mechanical systole of the corresponding beat; it was directly related to the initial pressure of the same beat. In atrial fibrillation with slower and more regular ventricular rate there was no correlation between these factors, and the results were very similar to those obtained in normal subjects with sinus arrhythmia. The possible mechanisms involved in these hemodynamic phenomena are discussed.

REFERENCES

1. Buchbinder, W. C., and Sugarman, J.: Arch. Int. Med. **66**:625, 1940.
2. Coblentz, B., Harvey, R. M., Ferrer, M. I., Cournand, A., and Richards, D. W., Jr.: Brit. Heart J. **11**:1, 1949.
3. Braunwald, E., Moscovitz, H. L., Amram, S. S., Lasser, R. P., Sapir, S. O., Himmelstein, A., Ravitch, M. M., and Gordon, A. J.: J. Appl. Physiol. **8**:309, 1955.
4. Eliakim, M., and Braun, K.: Am. Heart J. **51**:61, 1956.
5. Katz, L. N., and Feil, H. S.: Arch. Int. Med. **32**:672, 1923.
6. Wiggers, C. J.: Circulatory Dynamics, New York, 1952, Grune & Stratton, Inc.
7. Bazett, H. C., Cotton, F. S., Laplace, L. B., and Scott, J. C.: Am. J. Physiol. **113**:312, 1935.

ELECTROCARDIOGRAPHIC STUDIES ON FIBRILLATING AND NONFIBRILLATING HYPOTHERMIC DOGS WITH OR WITHOUT PREVIOUS TREATMENT WITH ACETYLCHOLINE OR PROCAINE AMIDE

KNUT HAEGER, M.D., BENGT JOHANSSON, M.D., AND BJÖRN SJÖSTRÖM, M.D.

MALMÖ, SWEDEN

UNCONTROLLABLE ventricular fibrillation (VF) can be considered the most important and dreaded complication in cooling both human beings and animals. It has also been shown[1] that it is more difficult to restore such fibrillation to the normal rhythm if the heart is at a hypothermic temperature than if it is at a normal one. It would therefore be desirable to find some method of preventing VF, that is by administering "antifibrillatory drugs." In animals at a normal temperature, it has been demonstrated that the tendency toward VF can be reduced by means of various drugs (a general survey to be found in articles by Di Palma and Schultz,[2] and by Wiggers[3]).

Certain attempts have been made to put these observations into practice in conjunction with hypothermia. Swan and associates[4] showed that the administration of both Prostigmin and acetylcholine had a pronounced antifibrillatory effect on the canine heart during hypothermia. The effect of Prostigmin was attributed to its anticholinesterase action. Haeger and Sjöström[5] demonstrated that administering procaine amide (Pronestyl) to hypothermic rabbits raised the threshold for electrically produced VF and also that VF appeared less often in dogs which had been cardiotomized in hypothermia when they had been pretreated with an infusion of Pronestyl in dextran solution.

We have investigated the electrocardiographic changes in three groups of dogs during hypothermia. One group was treated with Prostigmin and acetylcholine, a second with procaine amide, and a third group was used as a control without any previous treatment.

METHODS

Adult mongrel dogs of both sexes weighing between 20 and 35 kilograms were used. The animals were shaved over the greater part of the body and anesthetized with Nembutal (Abbott) intravenously in a dose so calculated that the eye reflex disappeared, after which they were intubated endotracheally. All dogs were hyperventilated with pure oxygen in a semiclosed system including carbon dioxide absorption throughout the experiment. Hypothermia was brought about by refrigeration with cold air circulating in a thermobox.[6]

From the Department of Experimental Surgery and the Cardiac Laboratory, Department of Medicine, University of Lund, Allmänna Sjukhuset, Malmö, Sweden.

Received for publication April 16, 1956.

At +28° C. deep rectal temperature the dogs were withdrawn from the box, after which the body temperature regularly sank a few degrees centigrade.

Standard three-limb lead electrocardiograms were obtained during the whole experiment for every fall in the temperature of one degree centigrade, or more often if changes were noticed during the direct cardioscopic observation. All electrocardiographic recordings were made with the animals in the left lateral position.

In a few isolated cases where shivering was noted this was immediately cured by administering a minimum dose (20 mg. at most) of succinylcholine iodide (Celocurin, Vitrum).

Group A: Acetylcholine-Prostigmin (4 dogs).—Simultaneously with the beginning of the refrigeration process a solution of 5 ml. 0.05 per cent Prostigmin and 0.0025 mg. acetylcholine per 1000 ml. dextran was given as intravenous drip infusion. The rate of the drops was regulated so that 10 ml. per kilogram of body weight was infused every hour.

Group B: Pronestyl (6 dogs).—At the same rate this group received an infusion of 400 mg. of procaine amide (Pronestyl, Squibb) per 1000 ml. dextran.

Group C: Control (9 dogs).—This group received only dextran in the same dose as the preceding groups.

RESULTS

1. *Heart Rate.*—The dogs in Group A had throughout a lower heart rate, averaging 84 beats per minute at 35° C. and 30 beats per minute at 25° C., than Group C, which at 35 °C. had on the average 159 beats per minute and at 25° C., 71 beats per minute; hence a reduction of approximately 50 per cent. The heart rate of the Pronestyl-treated dogs in Group B showed a wider individual spreading of values. Most often the values, however, were found to be between those of the other groups (see Fig. 1).

2. *Rhythm.*—Sinus rhythm dominated most often. There were no disturbances of rhythm at all in Group B. In Groups A and C extrasystoles emanating from different foci appeared in about half the experiments. Transient nodal rhythm also occurred in both these groups.

3. *P Wave.*—At the beginning of the period of decreasing temperature the mean duration of the P wave was 0.12 second in Group A and 0.06 second in Groups B and C, respectively. At +27° C. the corresponding values were 0.17 and 0.08 second, respectively. The Pronestyl-treated dogs in Group B showed a wider individual spreading of the values, otherwise there was no fundamental difference between those groups.

The amplitude of the P wave, as measured in Lead II, was variable. No certain changes of amplitude during refrigeration could be established. The Pronestyl-treated dogs constantly had a lower P amplitude (0.15 mv. at +37° C. and 0.11 mv. at +27° C.) than both the remaining groups between which no certain difference could be established and whose corresponding amplitudes averaged 0.32 and 0.40 mv., respectively.

"Initial P-notching"[7] began to appear in the Prostigmin-acetylcholine-treated animals already at 34 to 35° C., while the phenomenon was not seen in

the control dogs before 28 to 32° C. In three dogs in Group B there occurred no initial P-notching, while in the remaining dogs in this group it appeared at 29 to 32° C.

4. *P-R Interval.*—The changes in conduction time appear in Fig. 2. For comparison the figures in Table I are given.

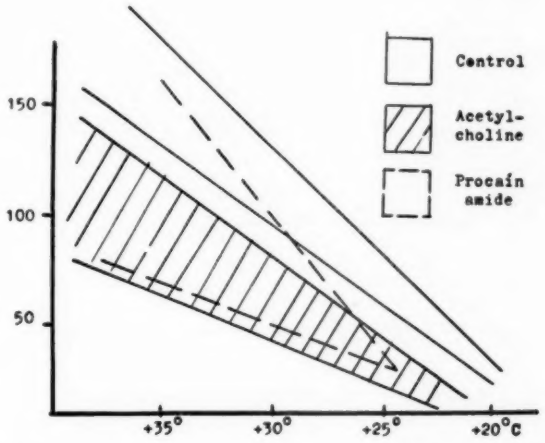


Fig. 1.—Heart rate at different temperatures from dogs untreated and treated with acetylcholine-Prostigmin and procaine amide. The straight lines approximately show the ranges of the three groups.

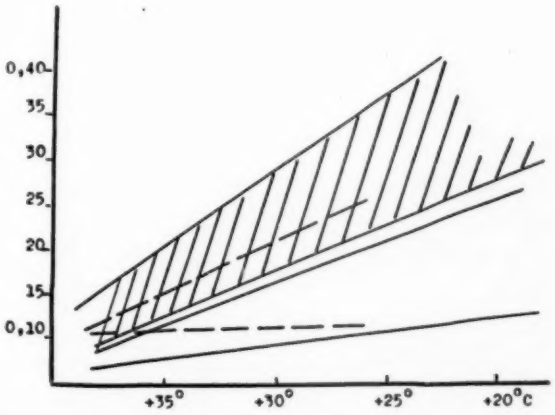


Fig. 2.—P-R intervals from dogs at different temperatures. See Fig. 1 for legend.

5. *QRS Complex.*—Average values of the duration of the QRS complex may be seen from Table II and Fig. 3.

Notching of the QRS complex appeared not infrequently. There was no difference between the various groups in this respect.

The QRS_{II} amplitude showed many great individual variations. The untreated dogs showed in eight out of nine cases a maximum at + 30° C. In the

Pronestyl-treated dogs this tendency was less pronounced and it did not exist at all in the acetylcholine-treated animals.

6. *Q-T Interval.*—Average values of the Q-T interval are to be found in Table III and Fig. 4.

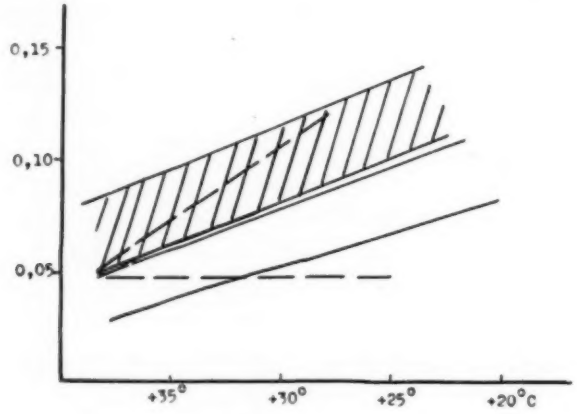


Fig. 3.—QRS intervals from dogs at different temperatures. See Fig. 1 for legend.

7. *ST-T Complex.*—"Osborn wave,"[7,8] a bow-shaped positive convex deformation of the transition between the QRS and ST-T complexes occurred in all the dogs in all three groups. In Group A it appeared regularly at 34 to 35° C., while in the other groups it might appear at any time during the period of refrigeration.

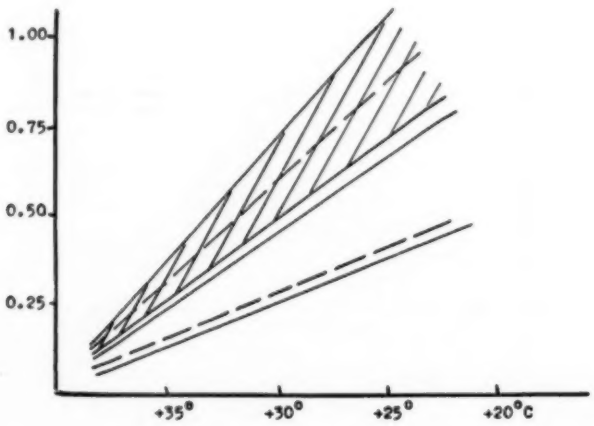


Fig. 4.—Q-T intervals from dogs at different temperatures. See Fig. 1 for legend.

There was no typical pattern with regard to T changes in any of the three groups. Nor was this the case with the S-T segments: in spite of attempts at systematizing by the division of the S-T segments in different types we could not find any differences between the groups. A contributory cause in this respect was the rapid fluctuation between different types of S-T segments in the

same dog within short intervals of time. For the same reason T changes could not be differentiated either.

TABLE I.

	+ 35° C. (sec.)	+ 25° C. (sec.)
Group A	0.18	0.30
Group B	0.11	0.18
Group C	0.09	0.15

TABLE II.

	+ 35° C. (sec.)	+ 25° C. (sec.)
Group A	0.08	0.13
Group B	0.06	0.10
Group C	0.06	0.09

TABLE III.

	+ 35° C. (sec.)	+ 25° C. (sec.)
Group A	0.39	0.92
Group B	0.27	0.58
Group C	0.22	0.47

DISCUSSION

In the untreated group there were noted, in short, the following electrocardiographic changes: slowing down of heart rate, and lengthening of P, P-R, QRS, and Q-T together with changes of S-T and T of varying kinds. Furthermore an "Osborn wave" appeared constantly. The main characteristics of these observations agree with those published earlier.[7,9-12]

In acetylcholine-treated animals at normal temperature (Prostigmin and acetylcholine cause similar electrocardiographic changes) the electrocardiogram shows sinus bradycardia, flattening of the P wave and P-notching, blocks of various kinds, relative shortening of the Q-T time, sometimes depression of S-T, and an increase of the T amplitude.[13,14] In our experiments, in the acetylcholine- and Prostigmin-treated dogs we observed bradycardia and a relative lengthening of P, P-R, QRS, and Q-T just at the beginning of the period of decreasing temperature. The P amplitude did not differ from that of the control group at corresponding temperatures. These observations differ, then, in certain respects from those of Goldenberg and Rothberger,[13] for example. P changes in the form of flattening or, with larger doses, of diphasic shape of the P, as described

by these authors, have not been observed by us. On the other hand we noted a relative prolongation of Q-T. This change was progressively accentuated during the course of hypothermia.

Szekely and Wynne[15] investigated the effect of procaine amide on the electrocardiogram of cats at normal temperature. To induce electrocardiographic changes in this species doses of 15 mg. per kilogram were required. At this dosage QRS was prolonged, S-T depressed, and the amplitude of T decreased; after larger doses rhythm irregularities appeared.

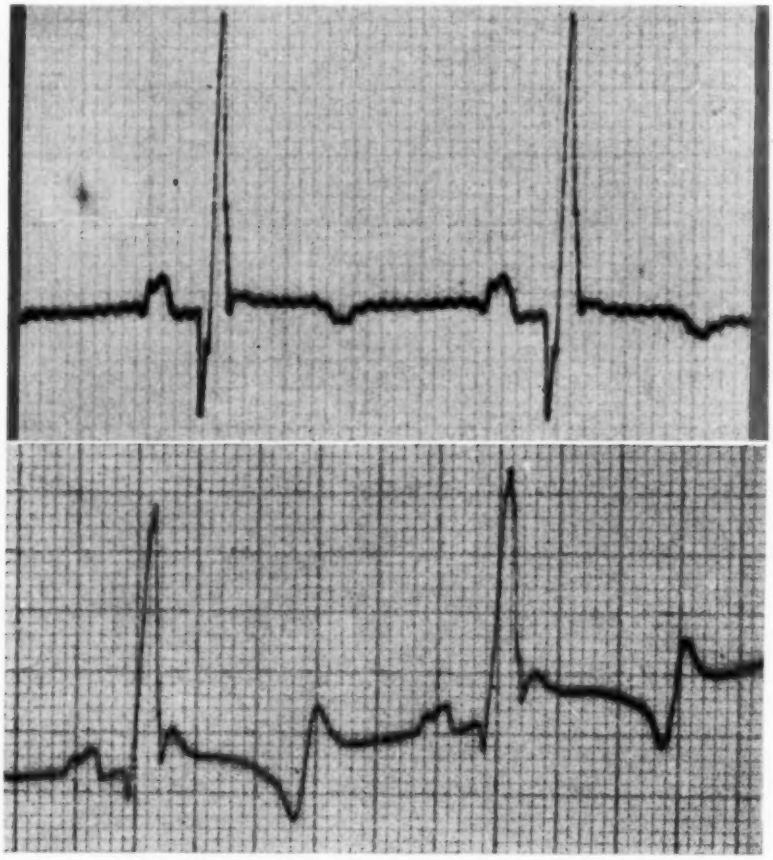


Fig. 5.—An ECG from the control Group C: (*A*), at 37.5° C., (*B*) at 28° C. Note the decrease of heart rate, prolongation of all the components of the ECG, and the large Osborn wave.

Shortly after the beginning of the period of decreasing temperature the heart rate of the Pronestyl-treated dogs was somewhat lower than that of the control animals. P-R and Q-T were prolonged. The changes in the QRS and the ST-T during refrigeration were similar to those in the control group which may be explained (provided that cats and dogs are directly comparable in this respect) by our lower dose of the drug. The low P amplitude which, throughout, occurred in the Pronestyl group and which remained during the whole period of hypothermia, is worthy of notice. During the entire course of the refrigerating procedure the heart rate was somewhat lower in this group, which might explain the somewhat prolonged P-R and Q-T times.

Summing up, it may be pointed out that the electrocardiographic changes which are caused by acetylcholine (Prostigmin) and procaine amide are principally the same at the beginning and the end of the refrigeration process. In hypothermia it appears that the changes which are regularly caused by the respective drugs are added to those caused by the hypothermia itself. This, however, is not so obvious regarding the changes in the S-T segment and T wave, for here the hypothermia itself exerts so strong an action that variations caused by the drugs administered are perhaps unable to manifest themselves.

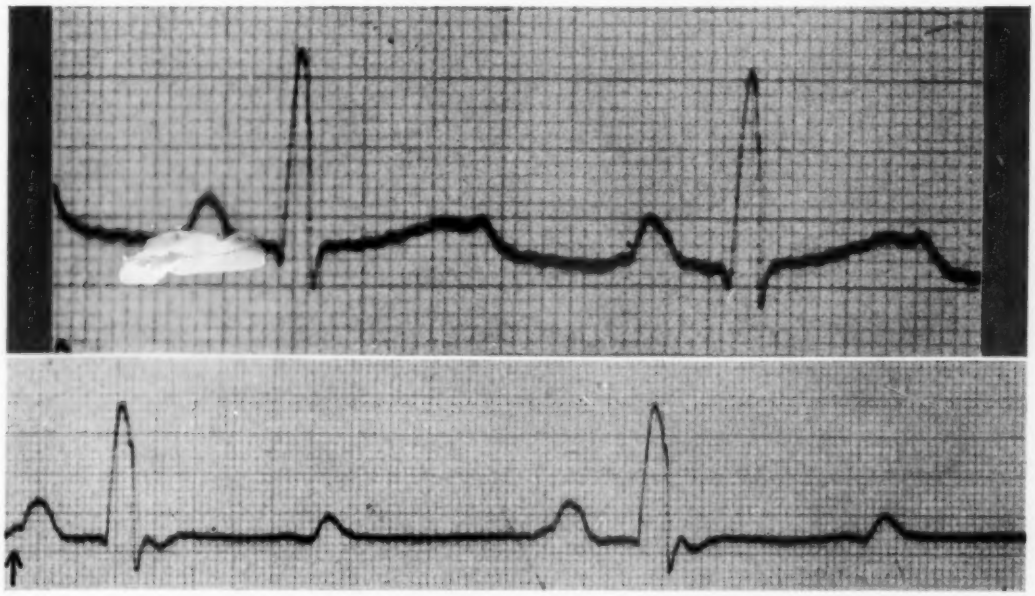


Fig. 6.—ECG from a dog treated with acetylcholine-Prostigmin at (*A*) 36° C. and (*B*) 26° C. The bradycardia and the prolongation of the different components are here more marked than in Fig. 5. Note the P notching (↑).

Low body temperature often potentiates the effect of a great number of various substances in the warm-blooded organism (review by Fuhrman[16]). The phenomenon has been observed in clinical medicine also. It has been demonstrated that acetylcholine, too, is subject to such a potentiation. As the temperature drops one ought consequently to have more pronounced acetylcholine-occasioned changes in the electrocardiogram; and this is in fact the case. The bradycardia, P-R, and Q-T durations became more pronounced in this group during the course of hypothermia than in the other groups. Also in the procaine amide-treated group the heart rate sinks relatively more rapidly than it does in Group C (control). As a consequence of this the P-R, QRS, and Q-T durations are comparatively longer at low than at normal temperature.

The most dreaded complication in hypothermia is ventricular fibrillation. We have tried in a retrospective survey of the electrocardiographic material to find some signs which might indicate the risk of the appearance of VF. Covino and associates[17] have pointed out the presence of differences in the stimulus

threshold for refrigerated dogs with and without later development of VF. Because of these observations we suspected that the ECG might give some hints as to the possibility of future fibrillation. For this reason, experiments were designed to provoke VF by submitting animals at temperatures of 25 to 28° C. to total exclusion of all blood to the venous half of the heart and simultaneously carrying out a right cardiotomy. Out of fourteen dogs operated upon in this fashion, in six cases VF appeared, all at a temperature not above 27° C. In no case VF occurred before the operation was commenced.

Milstein and Brock[18] describe three kinds of electrocardiographic changes which they consider indicate stages preliminary to VF in human beings: namely, (1) increased irritability in the form of ventricular extrasystoles and paroxysmal ventricular tachycardia; (2) signs of increasing myocardial depression in the form of bundle branch block and constantly increasing S-T depression with eventual bradycardia; and (3) asystole. Osborn[8] states that the wave described by him is a sign of bad prognosis, which, however, was not confirmed by Biörck and Johansson.[7] Siems and associates[19] consider that one can draw no conclusions about the eventual lethal outcome from electrocardiographic changes during hypothermia, and Bigelow and associates,[20] also hold the view that "there is usually little warning."

The comparison of the electrocardiographic series of those dogs which had not fibrillated, with the series of those which had, resulted in this: *we cannot point to any sign which indicated that VF was imminent.* Osborn waves appeared constantly in all the animals. None of the eleven different S-T types registered occurred more often in the animals with VF. The average value of the maximum S-T displacement was in all three leads somewhat higher in the group without VF; the same was true of the maximum T-amplitude variation. These changes are, however, hardly of such a significance that they may be taken as any sign for prognosticating VF. Extrasystoles were found in only one of the fibrillating dogs while this phenomenon occurred in more of the nonfibrillating ones (7 dogs). Neither can these changes, then, be used for prognosticating VF.

SUMMARY

1. The electrocardiographic changes in dogs submitted to deep hypothermia and different types of "antifibrillatory" treatment were investigated.

2. The ECG changes after treatment with acetylcholine-Prostigmin and procaine amide, respectively, are principally the same in the beginning and the end of the period of decreasing temperature. It was noted, however, that to these alterations were added some changes which probably may be attributed to hypothermia itself. The implications of these findings are discussed.

3. In a retrospective investigation with the aim to find out whether any signs could be detected that might be taken as a warning of impending ventricular fibrillation, we could not find any sign whatsoever pointing in that direction. Earlier investigations on this theme are reviewed briefly and the results are discussed.

We are greatly indebted to Dr. G. Biörck for critically reviewing this paper.

REFERENCES

1. Kirby, C., Jensen, J. M., and Johnson, J.: Arch. Surg. **68**:663, 1954.
2. Di Palma, J. R., and Schultz, J. E.: Medicine **29**:123, 1950.
3. Wiggers, C. J.: Circulation Research **1**:191, 1953.
4. Montgomery, A. V., Prevedel, A. E., and Swan, H.: Circulation **10**:721, 1954.
5. Haeger, K., and Sjöström, B.: Attempts to Prevent Ventricular Fibrillation in Hypothermia With "Antifibrillatory" Drugs, Swedish Society for Cardiology, 1955 (to be published).
6. Biörck, G., Damgaard-Nielsen, M., Haeger, K., Ryd, H., and Wulff, H. B.: Scandinav. J. Clin. Lab. Invest. **6**:277, 1954.
7. Biörck, G., and Johansson, B.: Acta. Physiol. scandinav. **34**:257, 1955.
8. Osborn, J. J.: Am. J. Physiol. **175**:389, 1953.
9. Bigelow, W. G., Lindsay, W. K., and Greenwood, W. F.: Ann. Surg. **132**:849, 1950.
10. Hegnauer, A. H., Shriber, W. J., and Haterius, H. O.: Am. J. Physiol. **161**:455, 1950.
11. Hook, W. E., and Stormont, R. T.: Am. J. Physiol. **133**:334, 1941.
12. Prec, O., Rosenman, R., Braun, K., Rodbard, S., and Katz, L. N.: J. Clin. Invest. **28**:293, 1949.
13. Goldenberg, M., and Rothberger, C. J.: Ztschr. ges. exper. Med. **94**:151, 1934.
14. Liebow, I. M., and Hellerstein, H. K.: Fed. Proc. **9**:77, 1950.
15. Szekely, P., and Wynne, N. A.: Brit. Heart J. **16**:267, 1954.
16. Fuhrman, F. A.: Physiol. Rev. **26**:247, 1946.
17. Covino, B. G.: Am. J. Physiol. **181**:553, 1955.
18. Milstein, B. B., and Brock, Sir Russel: Guy's Hosp. Rep. **103**:213, 1954.
19. Siems, M. V., Horvath, S. M., Spurr, G. B., Hutt, B. K., and January, L. E.: Am. J. Physiol. **181**:325, 1955.
20. Bigelow, W. G., Mustard, W. T., and Evans, J. G.: J. Thoracic Surg. **28**:463, 1954.

THORACIC AORTOGRAPHY

JOHN B. JOHNSON, M.D., JOHN W. LAWLAH, M.D., FREDERICK MCFADDEN, M.D., AND JOSEPH F. DYER, JR., M.D.

WASHINGTON, D. C.

WITH THE TECHNICAL ASSISTANCE OF AUDREY I. FAIRLEY AND VERA COLLINGS

THE rapid advances in the surgical management of mediastinal masses in general and of lesions of the upper thoracic aorta and its branches in particular, have greatly increased the need for accurate contrast visualization of all component segments of the intrathoracic aorta and its major branches. Satisfactory delineation of the ascending and transverse aorta is obtained by routine angiocardiography in about 65 per cent of the cases examined.[1] Angiocardiography is often unsuccessful in the visualization of the intrathoracic aorta in patients with enlarged hearts, in patients with delayed arm-to-tongue circulation time, and in patients with mediastinal masses which partially or completely obstruct the superior vena cava. In some instances, the lower thoracic aorta is well demonstrated by translumbar aortography using the method of Dos Santos and his associates.[2]

Aortography of the ascending aorta and the aortic arch, obtained by the retrograde injection of radiopaque media through polyethylene tubing has not been attempted on a large scale because of the constant danger of brain damage including hemiplegia, cerebellar disturbances, coma, and death.[3,4]

More recently, aortography of the lower thoracic aorta has been reported in which the contrast media were injected into the thoracic aorta through a special needle using a left anterior,[5] or a left posterior, transthoracic[6] approach. This method, however, does not obtain visualization of the ascending and transverse aorta or of the brachiocephalic arteries. Furthermore, the procedure requires general anesthesia and has the inherent hazard of pneumothorax and intrathoracic hemorrhage, although these complications were not observed in the groups of four and six patients reported by the respective authors cited above.

This paper reports our experience with contrast visualization of all component segments of the thoracic aorta and its major branches, by femoral artery catheterization-aortography using sodium and methylglucamine diacetylaminotriiodobenzoates (Renografin 76 per cent*). To date, we have given a total of 86 injections into or proximal to the aortic arch in eighteen patients without evidence of any type of brain damage and without any other important complications. In all instances, this procedure has been successfully completed without the need for general anesthesia.

From the Cardiovascular Laboratory of the Department of Medicine of Freedmen's Hospital and Howard University College of Medicine.

This study was supported in part by a grant-in-aid from Squibb Institute for Medical Research.
Received for publication March 8, 1956.

*Renografin 76 per cent was used exclusively in this study.

MATERIALS AND PROCEDURE

Necessary Equipment.—

1. An 11- or 12-gauge thin-wall trocar needle about 2 inches long with stylet.
2. Disposable polyethylene tubing, inside diameter 0.062 inch, outside 0.082 inch, cut at appropriate length according to the length of the torso of the patient.
3. A 17-gauge needle, filed blunt and a stopcock drilled out with a 3/32 inch drill for insertion into the external end of the polyethylene tube.
4. A 20 c.c. Luer-Lok syringe.
5. Sodium and methylglucamine diacetylaminotriiodobenzoates (Renografin 76 per cent).

Procedures.—

Catheterization of the aorta through the femoral artery as initially proposed by Farinas[7] and as described by Peirce,[8] forms the basis of the procedure used in this study. The patients presented in this report were adult subjects who came to the laboratory in a fasting state. About one hour prior to the study each patient was given 1½ grains of phenobarbital orally. The femoral triangle area was prepared with tincture Zephiran and infiltrated with 2 per cent Novocain.

The 11- or 12-gauge angiocardiogram needle was inserted into the femoral artery through a small skin incision. The polyethylene tube, filled with Renografin was rapidly threaded into the aorta for a distance estimated to be above the level of the diaphragm. At this point, the angiocardiogram needle was withdrawn from the femoral artery over the polyethylene tube, leaving the tube in place. One or two milliliters of Renografin injected at this stage serves as a sensitivity test dose. The tube, filled with contrast material, was then advanced under fluoroscopic control to the desired position in the thoracic aorta. We have routinely made the first injection with the catheter tip proximal to the aortic arch well into the ascending aorta. Subsequent injections were made with the catheter tip advantageously located with reference to the particular lesions of the aorta under study. Twenty to thirty milliliters of Renografin injected manually with maximum rapidity using a 20 c.c. Luer-Lok syringe was found to be satisfactory for opacification of the section of thoracic aorta in question. Exposures were made at the rate of 2 per second for three to four seconds using the Fairchild roll film cassette beginning with the onset of injection. At least two injections were made in all patients. When the single film exposure technique was used, utilizing 14 by 17 inch films, additional injections were usually necessary in order to obtain accurate delineation of the abnormality in question.

Initially, all patients accepted for study had important diagnostic problems involving mediastinal masses in which there was question of aneurysm. The study was designed to give precise information as to location, configuration, and extent of the aneurysm. After repeated injections of Renografin were found to be completely free of demonstrable brain injury or other important sequelae, several patients were studied in whom the thoracic aorta was thought to be normal. The number of patients studied, their age ranges, the number of injections given each patient, and the type of reaction observed are summarized in Table I.

TABLE I. SUMMARY OF CASES INCLUDING AGE, NUMBER OF INJECTIONS, AND TOXIC REACTIONS

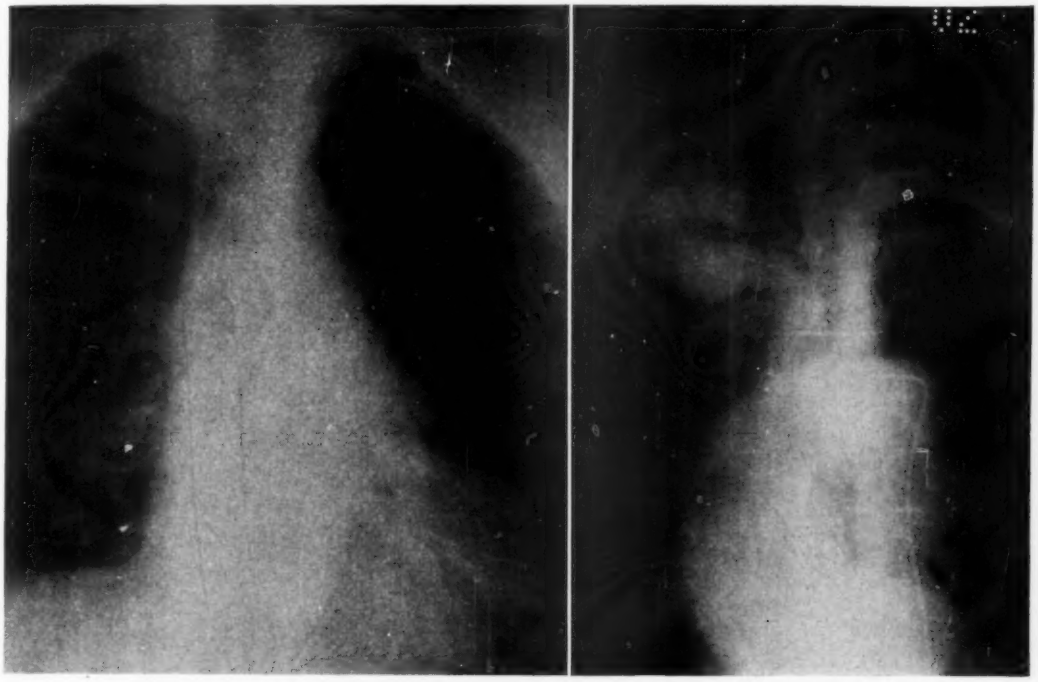
CASE NUMBER	AGE	NUMBER OF INJECTIONS	TOXIC REACTIONS AND COMPLICATIONS
1 (L.H.)	74 (F)	3	Slight nausea after first injection
2 (P.B.)	67 (F)	6	No cerebral symptoms or signs immediately or during ten-day follow-up period
3 (H.C.)	40 (M)	6	No cerebral symptoms or signs immediately or during ten-day follow-up period
4 (H.C.)	73 (M)	4	No reaction
5 (N.L.)	50 (F)	3	Emesis after second injection
6 (R.S.)	76 (M)	2	"Hot and dizzy" after both injections. Patient had slight vertigo on assuming erect position for several days following aortography which cleared completely.
7 (T.B.)	46 (M)	4	No reaction
8 (B.B.)	37 (F)	5	No cerebral or coronary symptoms
9 (L.U.)	47 (F)	4	No reaction
10 (A.H.)	75 (M)	4	No reaction
11 (W.W.)	78 (M)	5	No reaction
12 (M.P.)	56 (F)	4	No reaction
13 (M.M.)	61 (F)	7	No reaction
14 (G.W.)	86 (M)	10	No reaction
15 (F.F.)	53 (M)	9	No reaction
16 (J.J.)	79 (M)	4	Pain after injection into aorta near the area of the renal arteries
17 (N.B.)	22 (F)	2	No cerebral symptoms or signs immediately or during ten-day follow-up period
18 (L.I.)	59 (M)	4	No reaction
Total		86	

Angiographic clarification of superior mediastinal masses suspected as lesions of the brachiocephalic arteries: Lesions of varying size involving the superior mediastinum are frequently seen in the routine posteroanterior chest film. In adults, when such lesions involve the innominate artery or its branches, the angiocardiogram may not be successful in clarifying the lesion. In some instances the lesion may be so located as to partially obstruct the superior vena cava and prevent rapid opacification of the heart and aorta. Retrograde thoracic aortography using Renografin in our hands has been found a safe and effective method which clearly differentiates the vascular or nonvascular nature of such lesions.

CASE 6 is that of a 76-year-old man in whom the routine chest film preparatory to prostatectomy showed an opacity to the right of the manubrium. Thoracic aortography demonstrated the lesion to be a small aneurysm at the distal end of the innominate artery (Fig. 1, *A* and *B*). CASE 2 was that of a 67-year-old woman admitted with a diagnosis of superior vena caval syndrome probably due to a large aneurysm of the innominate artery (Fig. 2, *A*). The tumor mass was not expansile under fluoroscopic observation; however, a laminated clot in a large aneurysmal sac could not be excluded and had to be considered in the differential diagnosis. Angiocardiography failed to demonstrate the nature of the lesion, but instead demonstrated bilateral innominate vein obstruction with massive collateral circulation (Fig. 2, *B* and *C*). Retrograde thoracic aortography with Renografin demonstrated intact brachiocephalic arteries and nonopacification of the tumor mass (Fig. 2, *D*). At operation the lesion proved to be a large substernal thyroid adenoma which was completely encapsulated and relatively easily excised. This

patient had been denied surgical therapy for a number of years on the advice of her physicians who agreed unanimously that this lesion was a large aneurysm of the ascending aorta, aortic arch, and innominate artery.

Visualization of the root of the aorta including the aortic valve and brachiocephalic arteries: The root of the pulmonary artery and the pulmonary valve are frequently well delineated in adults using angiocardiography. On the other hand, the aortic valve and the root of the aorta are seldom well defined by angiocardiography. In retrograde aortography, as reported in this paper, the tip of the catheter is readily placed at the root of the aorta, except in the large



A. *B.*

Fig. 1.—*A*, Triangular density below medial end of right clavicle. *B*, Catheter in aortic arch. Angiogram demonstrating the triangular density to be saccular dilatation of terminal portion of innominate artery. Right common carotid well outlined.

tortuous aorta or in those with multiloculated aneurysmal sacs. Rapid injection of 20 c.c. of the Renografin solution at this point allows well-defined opacification of the ascending aorta and aortic valve. Fig. 3 shows the root of the aorta including aortic valve, the ascending and transverse aorta, and the brachiocephalic arteries in Case 9, a 47-year-old woman with a history of convulsive seizures but without evidence of heart disease.

Visualization of the descending thoracic aorta: Lesions involving the mediastinum below the level of the aortic arch often present diagnostic problems which may be clarified by retrograde aortography.

CASE 4 is that of a 73-year-old man who was being considered for surgery for operable cancer of the prostate gland. The posteroanterior chest film (Fig. 4, *A*) showed a smooth mass, thought

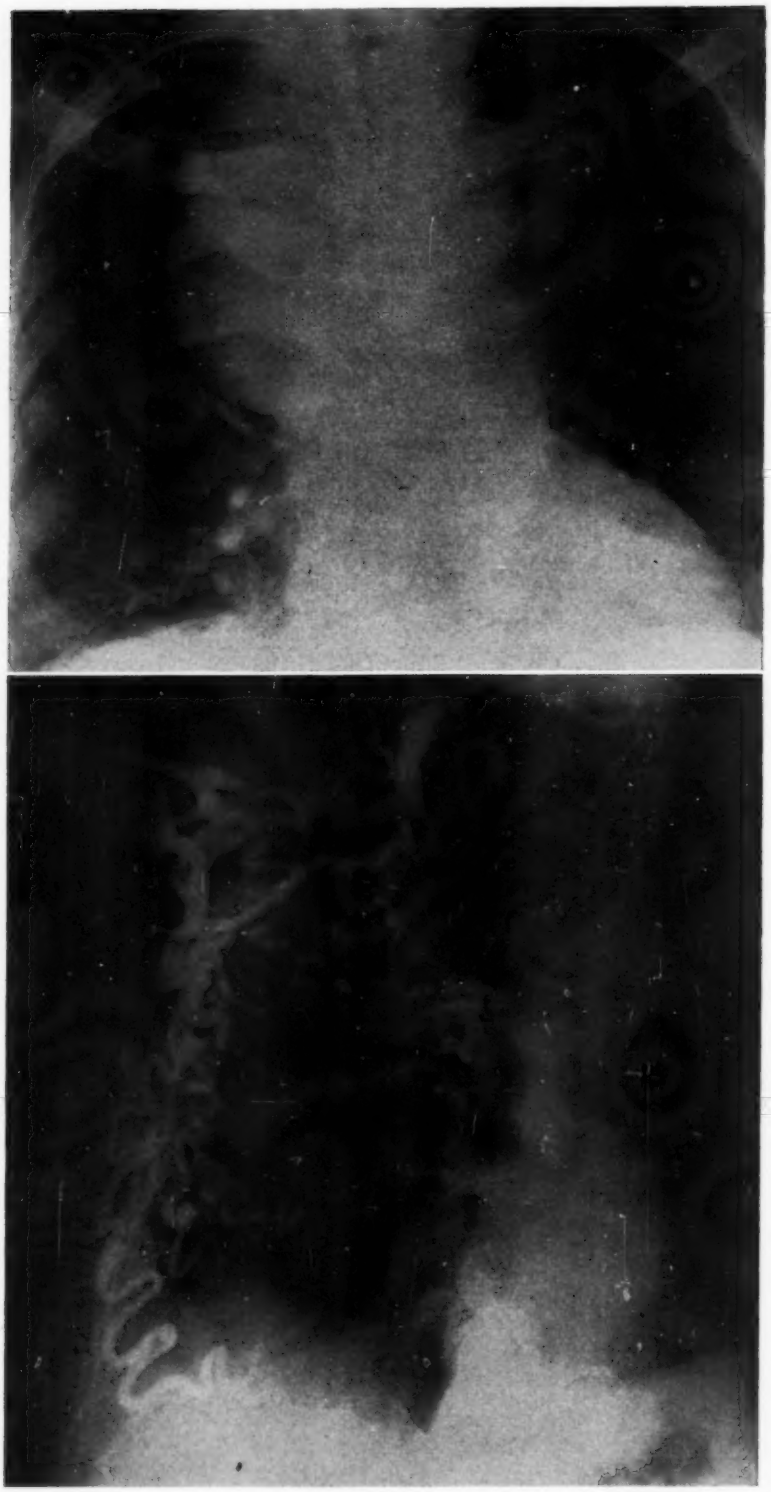
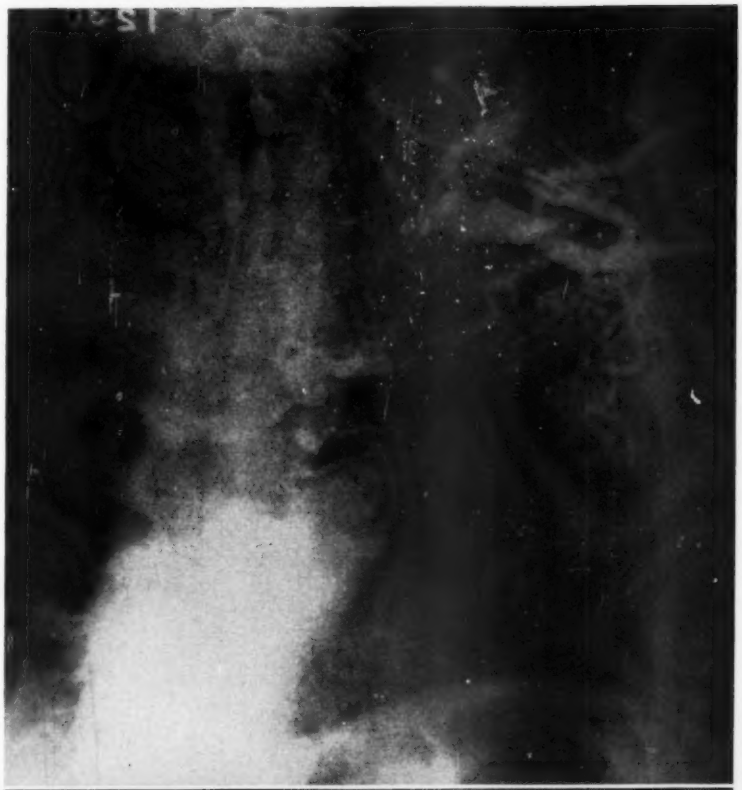
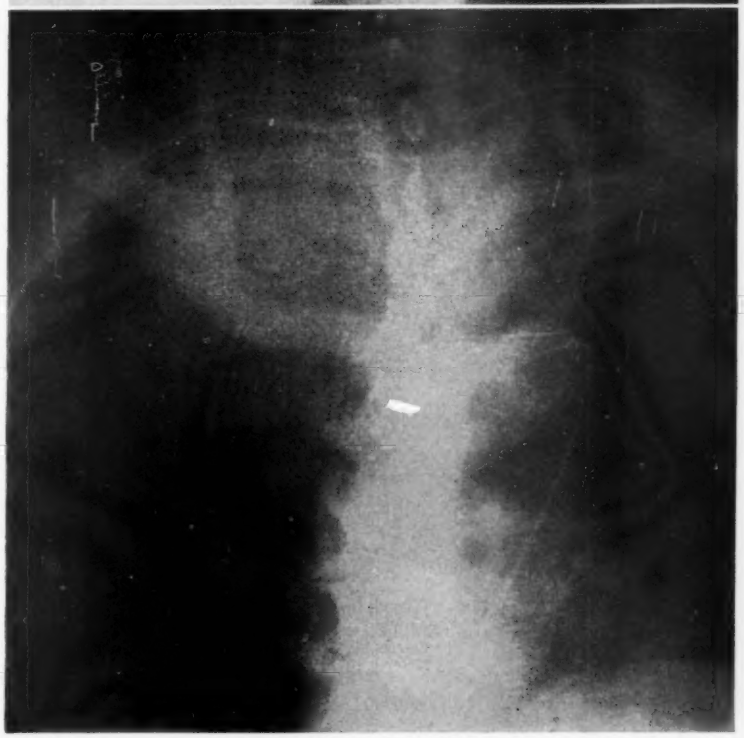


Fig. 2.—*A*, Control posterior-anterior film of chest showing large rounded mediastinal density which could not be separated fluoroscopically from the heart and brachiocephalic arteries. *B* and *C*, Angiocardiograms done from the right and left antecubital veins, respectively, demonstrating complete obstruction of innominate veins. The mass and brachiocephalic arteries were not visualized.

(Cont'd on opposite page.)



C.



D.

(Cont'd from opposite page.)

Note extensive collateral circulation and massive enlargement of internal mammary veins. *D*, Retrograde aortogram demonstrating laterally displaced, but intact, brachiocephalic arteries with nonopacification of mediastinal mass. At operation, mass excised and found to be large substernal thyroid adenoma.

to be an aneurysm of the thoracic aorta, along the right cardiac border. Surgery was deferred pending cardiovascular evaluation. Retrograde aortography demonstrated the structure to be a slightly dilated and elongated descending thoracic aorta and a right aortic arch (Fig. 4, *B*). Fig. 4, *C* shows the lower thoracic and upper abdominal aorta as obtained with retrograde aortography. Accordingly, prostatic surgery was performed since aneurysm of the aorta was excluded.

Visualization of the abdominal aorta and its branches: Using Renografin, it is safe and practical to delineate clearly the entire aorta by the retrograde procedure outlined above. Fig. 5 demonstrates the aorta from the middle of the thorax to a point distal to the origin of the celiac artery and its branches.

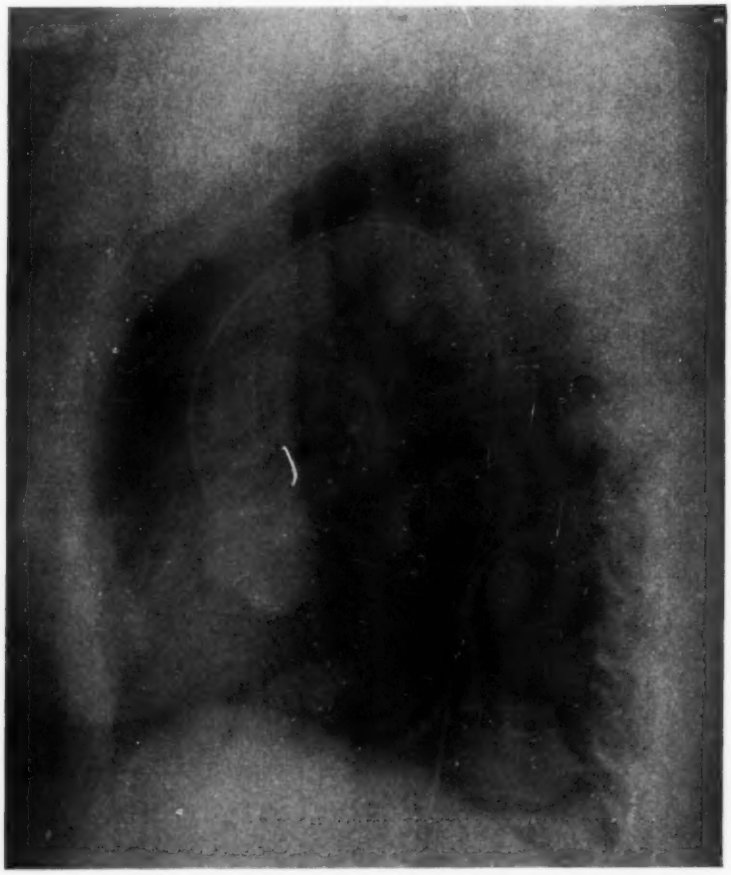
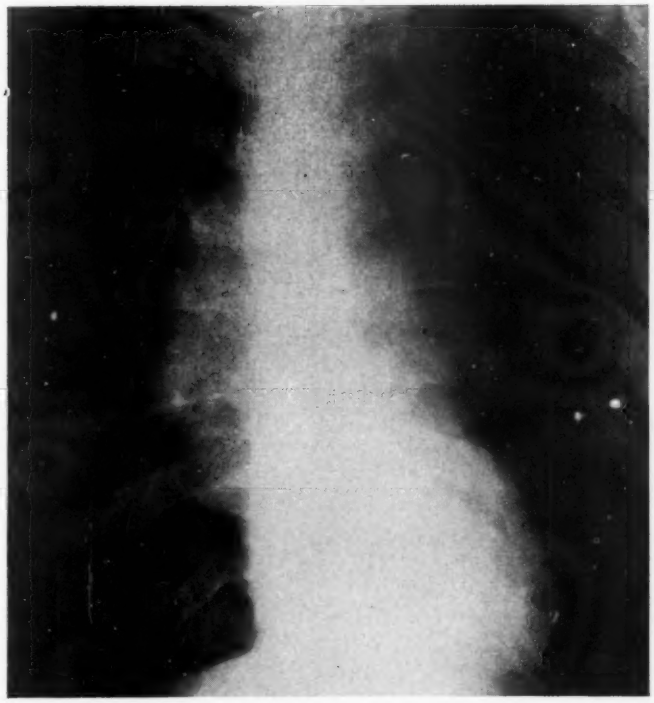
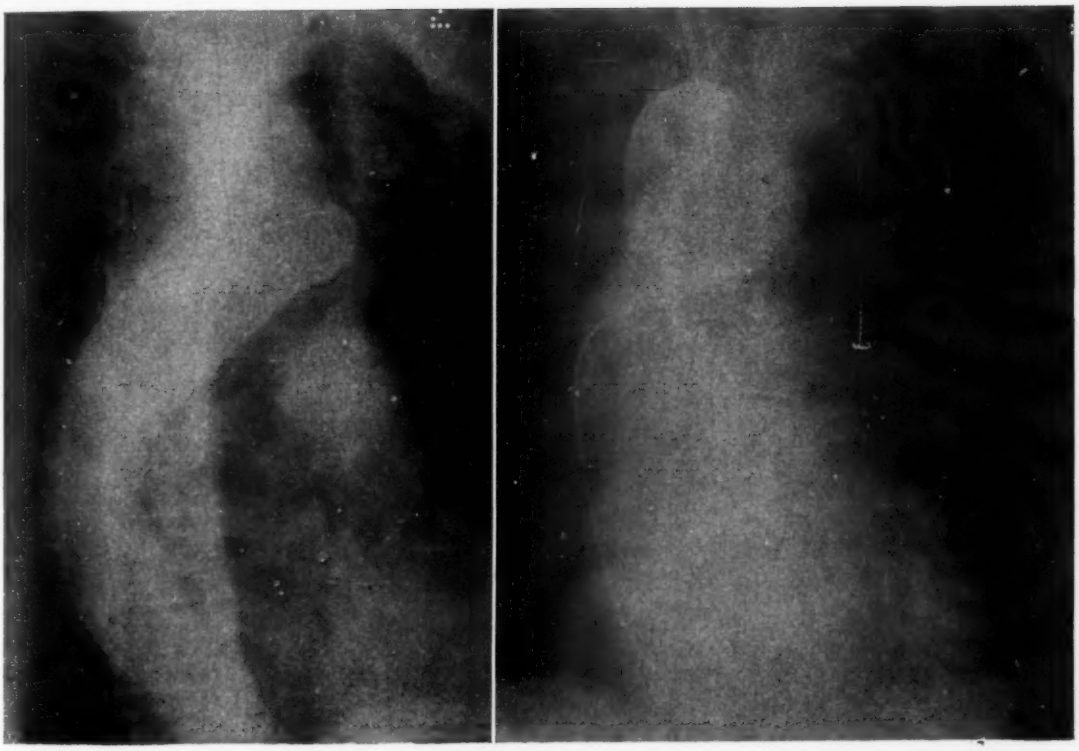


Fig. 3.—Retrograde aortogram showing root of aorta including region of semilunar valves, ascending and transverse aortic arch. Innominate artery well outlined.

Lesions of the terminal aorta may be clearly delineated by retrograde aortography providing one of the femoral arteries is free of obstruction. Fig. 6 illustrates arteriosclerotic obstruction of the right common iliac artery as demonstrated by retrograde aortography. The patient was a 40-year-old man with severe intermittent claudication of the right thigh and impotence. The lesion was excised and replaced by a "Y" arterial homograft with complete relief of intermittent claudication.

A.





B. *C.*

Fig. 4.—*A*, Posterior-anterior film of the chest showing enlargement of mediastinum to the right just above level of right auricle. *B*, Retrograde passage of catheter outlining course of thoracic aorta demonstrating right aortic arch. *C*, Retrograde aortogram showing thoracic aorta elongated but free of sacular dilation.

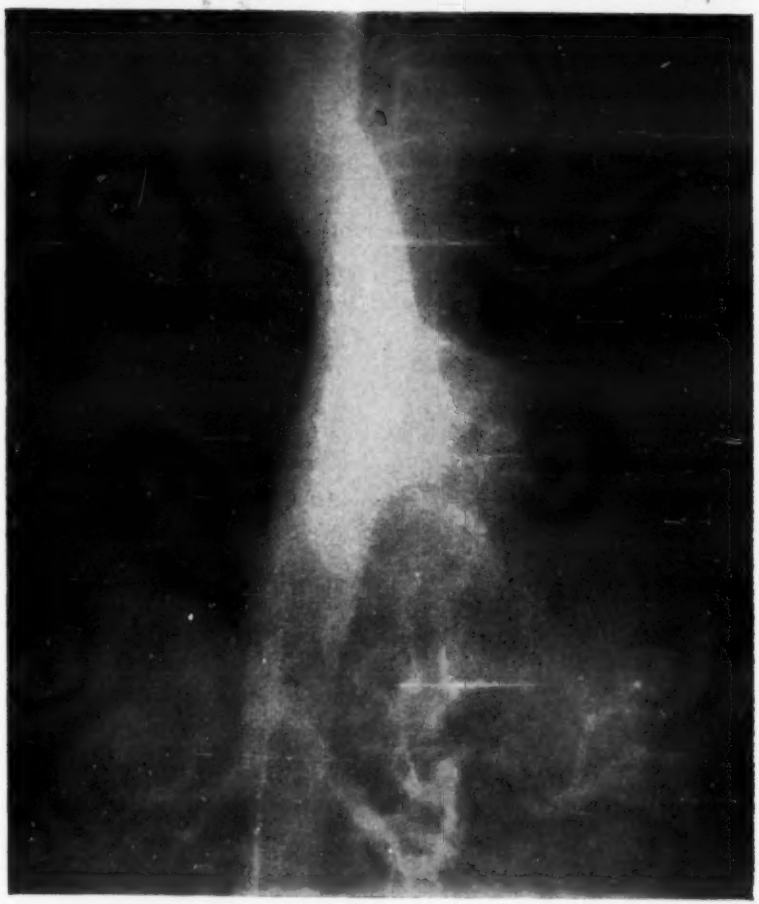


Fig. 5.

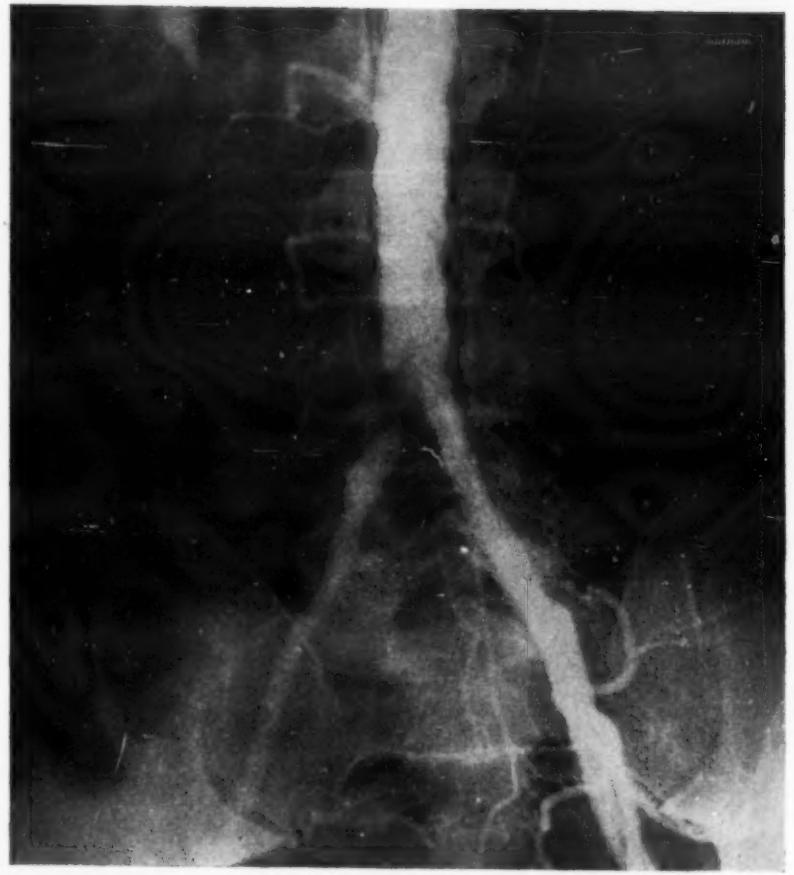
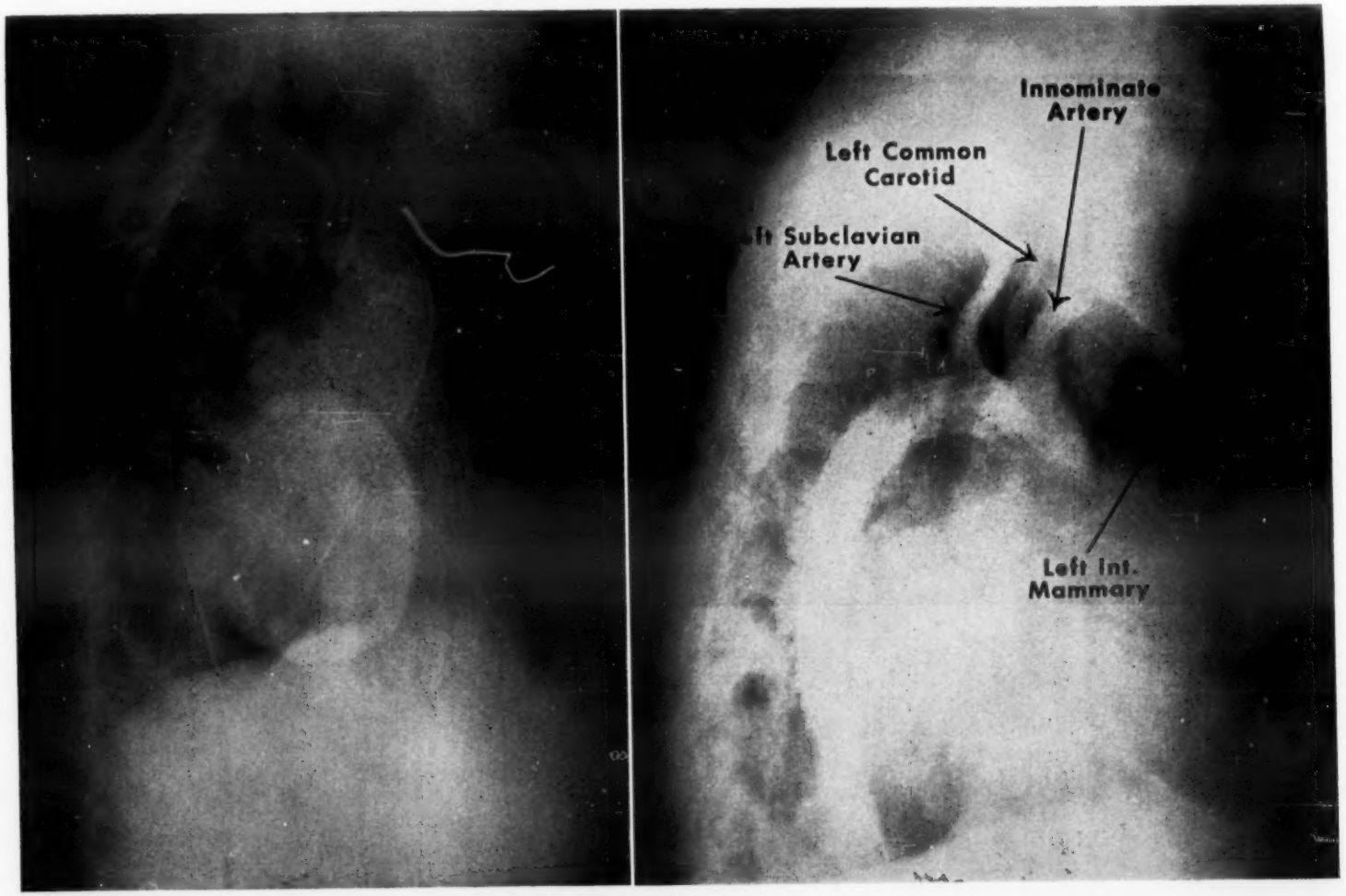


Fig. 6.

Fig. 5.—Retrograde aortogram showing descending aorta from mid-thoracic vertebrae to a point distal to the celiac artery and its branches.

Fig. 6.—Retrograde aortogram showing severe stenosis of the right common iliac artery at level of bifurcation of aorta. Terminal aorta excised and replaced by "Y" graft. Surgical specimen showed severe occlusive atherosclerosis.



A. *B.*

Fig. 7.—*A*, Catheter tip in left ventricle. Ventriculogram showing detailed outline of left ventricle. Neither ventricular chamber could be outlined by angiocardiography in this patient with severe right heart failure. *B*, Detailed outline of aortic arch and brachiocephalic arteries in same patient after catheter was withdrawn into the aorta.

Other observations which may be made utilizing retrograde thoracic aortography: In occasional cases, as the catheter passes freely into the ascending aorta, fluoroscopy demonstrates the tip of the catheter to have inadvertently slipped into the left ventricle. Renografin injection at this time will demonstrate a clear outline of the left ventricle. Fig. 7,*A* demonstrates one such instance (Case 3) in our series. After the catheter was retracted into the aorta, a second injection outlines the aortic arch and brachiocephalic vessels as well as the left internal mammary artery (Fig. 7,*B*). The advantage of this procedure over angiocardiography in the delineation of the aorta is especially well demonstrated in this patient with severe heart failure. The circulation was so prolonged (38 seconds) that no clear definition was obtained either of the pulmonary artery or of the aorta with standard angiocardiography.

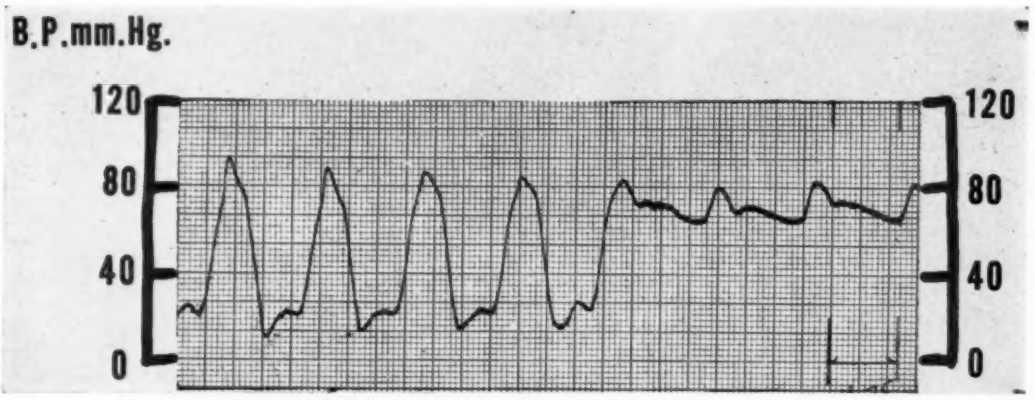


Fig. 8.—Left ventricular and aortic pressure curves during retrograde aortography.

In some cases of this group it has been possible to demonstrate the outline of the coronary arteries as illustrated in Fig. 3. The method should be satisfactory in the delineation of aorticopulmonary shunts since the aortic valve area can be clearly delineated. Visualization of an uncomplicated patent ductus should also be achieved by this method. We have not had occasion to observe such cases since this study was begun.

In those instances in which the tip of the catheter is found to be in the left ventricle, important hemodynamic information may be obtained. Fig. 8 demonstrates the left ventricular and aortic pressure curves in Case 3.

In some instances the catheter may be placed in the innominate or carotid arteries in which case delineation of the vertebral and cerebral arteries may be achieved.

Genitourinary tract screening should be a routine procedure in all cases of aortography as recommended in angiocardiography.[9]

SUMMARY

Contrast visualization of the ascending and transverse aorta and of the brachiocephalic arteries has not been reliable by angiocardiography. It has

not been attempted on a large scale by direct aortography methods because of the constant danger of brain damage.

This paper reports a study of contrast visualization of the ascending and transverse aorta by retrograde technique using sodium and methylglucamine diacetylaminotriiodobenzoates (Renografin 76 per cent). Eighty-six injections have been made with safety in eighteen patients successfully and without the need of general anesthesia.

Using the procedure and materials described, it has been possible to outline the root of the aorta, including the aortic valve, the aortic arch, and its branches, accurately as well as the remainder of the thoracic and abdominal aorta. The procedure has greatly improved the delineation of the vascular nature of masses associated with the root of the aorta, the aortic arch, and the brachiocephalic arteries.

Other observations which may be made using retrograde thoracic aortography include visualization of the coronary, vertebral, and cerebral arteries. In occasional instances hemodynamic data with reference to the left ventricle may be obtained when the catheter tip slips easily into the left ventricle.

REFERENCES

1. Neuhauser, E. B. D.: New England J. Med. **242**:753, 1950.
2. Dos Santos, R., Lamas, A., and Pereira Caldas, J.: Bull. Soc. Nat. Chir., Par. **55**:587, 1929.
3. Freeman, N. E., Fullenlove, T. M., Wylie, E. F., and Gilfillan, R. S.: Ann. Surg. **130**:398, 1949.
4. Peirce, E. C.,II: Circulation **7**:385, 1953.
5. Meneses Hoyos, J., and Gomez Del Campo, C.: Radiology **50**:211, 1948.
6. Pender, J. W., Kirklin, J. W., and Davis, G. D.: J.A.M.A. **159**:1738, 1955.
7. Farinas, P. L.: Am. J. Roentgenol. **46**:641, 1941.
8. Peirce, E. C., II: Surg., Gynec. & Obst. **93**:56, 1951.
9. Lawlah, J. W., Johnson, J. B., Fairley, A. I.: J.A.M.A. **158**:921, 1955.

RELATIONSHIP OF THE Q-T INTERVAL TO THE AVERAGE VENTRICULAR RATE IN AURICULAR FIBRILLATION

JACK MARGOLIS, M.D.*

BIG SPRING, TEX.

IT IS usually stated in the electrocardiographic texts and in papers dealing with the Q-T interval that this interval, besides being influenced by age, sex, drugs, diseases, and various other factors is primarily a function of the previous cycle length (R-R).

The formulae devised for whether a Q-T interval is normal or abnormal frequently employ a constant times the square root of the previous cycle length. This constant varies with different authors but the results usually approximate each other.

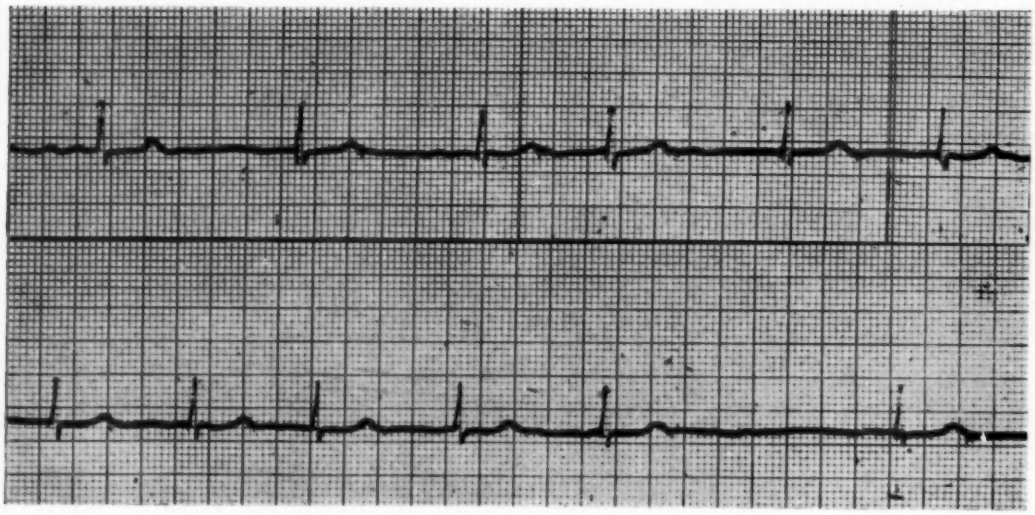


Fig. 1.—This is Lead II of a patient with auricular fibrillation showing wide variations in cycle length (R-R) with a relatively constant Q-T interval (maximum variation .04 of a second).

It is stated or implied in electrocardiographic texts that the shorter the diastole preceding a beat (short cycle length), the shorter the electrical systole (Q-T). It is also usually noted that this is a phenomenon changing from beat to beat. This was not found to be the situation in auricular fibrillation.

In auricular fibrillation the R-R interval may vary greatly, yet the Q-T interval rarely varies by more than 0.04 of a second. Frequently the Q-T interval remains constant even with large variations in previous cycle length (Fig. 1).

Received for publication Feb. 28, 1956.

*Medical Service, Veterans Administration Hospital, Big Spring, Tex.

When the average ventricular rate is determined in auricular fibrillation and the average Q-T measured, a curve can be made which closely approximates the R-R : Q-T relationships in sinus rhythm as previously worked out by many authors (Fig. 2).

Thus, it seems that whereas most formulas used in determining whether a Q-T interval is normal or abnormal employ the preceeding R-R interval and imply from this that this is a phenomenon changing from beat to beat, actually, in auricular fibrillation and perhaps in other arrhythmias with changing R-R intervals, the Q-T interval is dependent on the average ventricular rate and not on the previous cycle length.

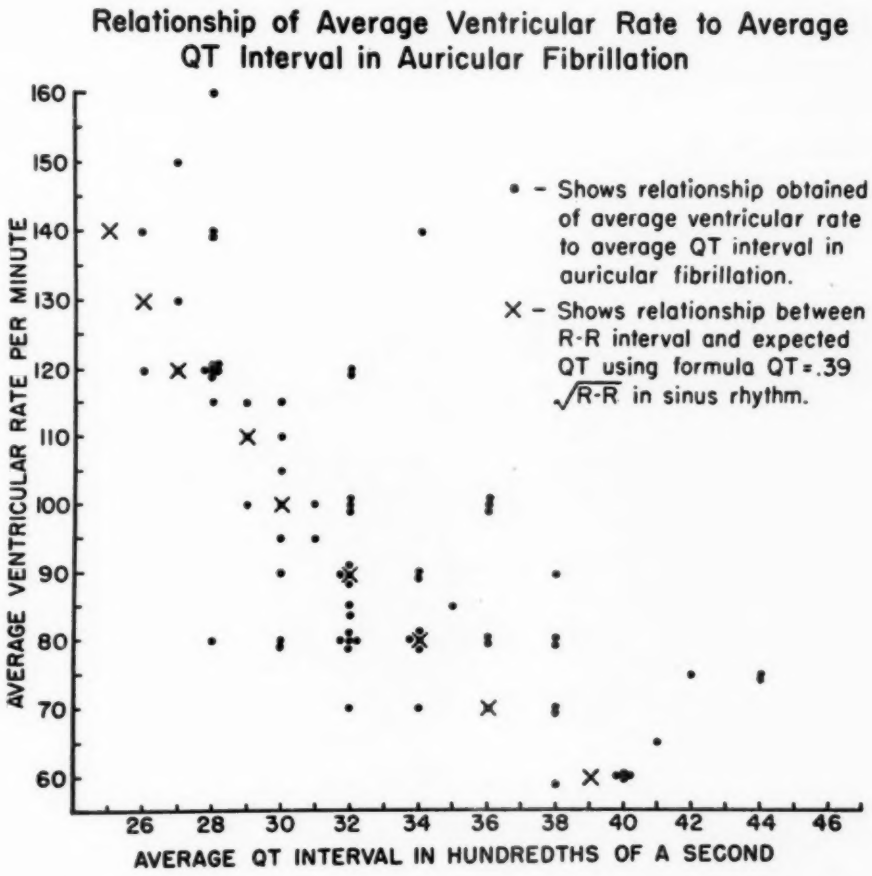


Fig. 2.—The chart shows the relationship of the average ventricular rate to the average Q-T interval in auricular fibrillation. For comparison, the "x's" on the chart show the relationship of the R-R interval and expected Q-T interval using the formula of Hegglin and Holzmann, where Q-T = .39 $\sqrt{\text{R-R}}$.

When the average ventricular rate is determined in auricular fibrillation and this is used instead of the previous cycle length, apparently the carefully prepared charts relating cycle length to Q-T interval in regular sinus rhythm can be used satisfactorily in auricular fibrillation for determining whether a Q-T interval is normal or abnormal.

REFERENCES

1. Katz, Louis N.: Electrocardiography, Ed. 2, Philadelphia, 1946, Lea & Febiger.
2. Goldberger, E.: Unipolar Lead Electrocardiography and Vectorcardiography, Ed. 3, Philadelphia, 1953, Lea & Febiger.
3. Burch, George E., and Winsor, T.: A Primer of Electrocardiography, Philadelphia, 1945, Lea & Febiger.
4. Ashman, R., and Hull, E.: Essentials of Electrocardiography, Ed. 2, New York, 1941, The Macmillan Company.
5. Pardee, Harold E. B.: Clinical Aspects of the Electrocardiogram, New York and London, 1948, Paul B. Hoeber, Inc.
6. Barker, J. M.: The Unipolar Electrocardiogram, New York, 1952, Appleton-Century-Crofts, Inc.

A QUANTITATIVE STUDY OF THE ELECTROCARDIOGRAPHIC EFFECTS OF ATRIAL ENLARGEMENT

J. A. Abildskov, Captain (MC) USAR*

Fort Bliss, Tex.

THE occurrence of abnormal P waves in association with atrial enlargement is a well-known and clinically useful finding. It is also well known that atrial enlargement may exist without producing recognizable abnormalities in the ECG. More reliable evidence of the presence and degree of enlargement of the atria and more precise differentiation of right and left atrial enlargement would be extremely useful in the differential diagnosis of cardiac lesions. It seems likely that improved methods of recording ECG data may help to provide such information and more detailed knowledge of the ECG effects to be expected from atrial enlargement will be of assistance in recognizing this information. This study was undertaken as a step in defining the ECG effects of varying degrees of atrial enlargement.

METHODS AND MATERIALS

The general method employed in this study consisted of the derivation of P waves from casts of the interior of human atria, employing means of analysis appropriate to the propagation of waves on a surface. The casts were prepared from autopsy specimens by ligating all communicating vessels close to the heart. Prior to ligating the superior vena cava and one pulmonary vein, the two sides of the heart were filled with liquid plaster of Paris. The plaster was allowed to harden with the specimen in such a position that external pressure did not alter the shape of the distended atria. The atria were then dissected free of the casts and the atrial portions of the casts broken from the ventricular portions. Right and left atrial casts were cemented together preserving their anatomic relationship. Atrial casts from four normal hearts were used in this study.

On each mold concentric lines representing the spread of activation were inscribed 1 cm. apart about the point marking the anterior margin of the junction of superior vena cava and right atrium. The models were then placed in their anatomic position using teleroentgenograms obtained during life and sketches and photographs made at the time of autopsy as guides to their orientation. In this position the anterior and posterior surfaces of the casts were photographed and the activation lines appearing in the photographs were used to derive P loops and P waves.

From the Cardiovascular Service, Department of Medicine, William Beaumont Army Hospital, Fort Bliss, Tex.

Received for publication March 8, 1956.

*Present address: State University of New York, College of Medicine, Syracuse, N. Y.

The method of deriving P loops and waves employed has been previously reported and its justification and sources of error discussed.[1,2] Vectors were placed normal to lines joining the two ends of each activation line and given magnitudes proportional to the distances between the two ends of the activation lines. The mirror image of vectors derived from the posterior surfaces of the atrial casts were obtained and all vectors were given a common origin. Those vectors derived from simultaneous activation lines were added vectorially and the termini of the final vectors were joined to give figures analogous to P loops of the vectorcardiogram. Projections of these loops on the sides of an equilateral triangle were obtained to give waves analogous to the P waves in the standard leads of the ECG. As previously reported P waves derived by this method were compared to those in ECG's actually recorded prior to death of the patients from whom the atrial casts were prepared and the general contour and relative magnitudes of the waves were similar.[2]

In this study enlargements of the photographs of atrial casts corresponding to 20, 40, 60, 80, and 100 per cent increase in linear dimensions were prepared. These increases in linear dimensions corresponded to increases in volume up to 800 per cent. Each atrium on each of these enlarged photographs was traced together with the activation lines appearing on that photograph and was paired with a tracing of the opposite natural-sized atrium and its activation lines. In placing the tracings of each enlarged atrium together with the nonenlarged atrium the same anatomic relations which existed between the two nonenlarged atria were preserved. With activation lines on the tracings of normal and enlarged atria as guides, it was possible to inscribe new activation lines 1 cm. apart as they would have appeared on atrial casts showing each of the degrees of enlargement studied. From these activation lines P loops and P waves were derived by the method described.

RESULTS

Right Atrial Enlargement.—The most evident change in P loops with progressive right atrial enlargement was an increase in length of vectors. This increase in vector magnitude was not linear with the degree of enlargement. The maximal vector increased 20 per cent in length with 20 per cent enlarge-

TABLE I. VCG CHANGES WITH RIGHT ATRIAL ENLARGEMENT

DEGREE OF ENLARGEMENT (%)	INCREASE IN LENGTH OF AVERAGE MAXIMAL VECTOR (%)	AVERAGE INCREASE IN TOTAL DURATION (%)	AVERAGE INCREASE IN APPARENT DURATION (%)
20	20	17	30
40	35	28	40
60	42	47	57
80	53	50	63
100	63	78	93

ment of the right atrium, but only 63 per cent with 100 per cent enlargement of that atrium. The increase in magnitude of maximal P-loop vectors with varying degrees of right atrial enlargement is summarized in Table I.

The total duration of atrial activation increased to a maximum of 78 per cent with 100 per cent enlargement of the right atrium. Increases in duration of activation were not linear with the degree of enlargement since the site of impulse origin had a different relation to the atria in the various degrees of

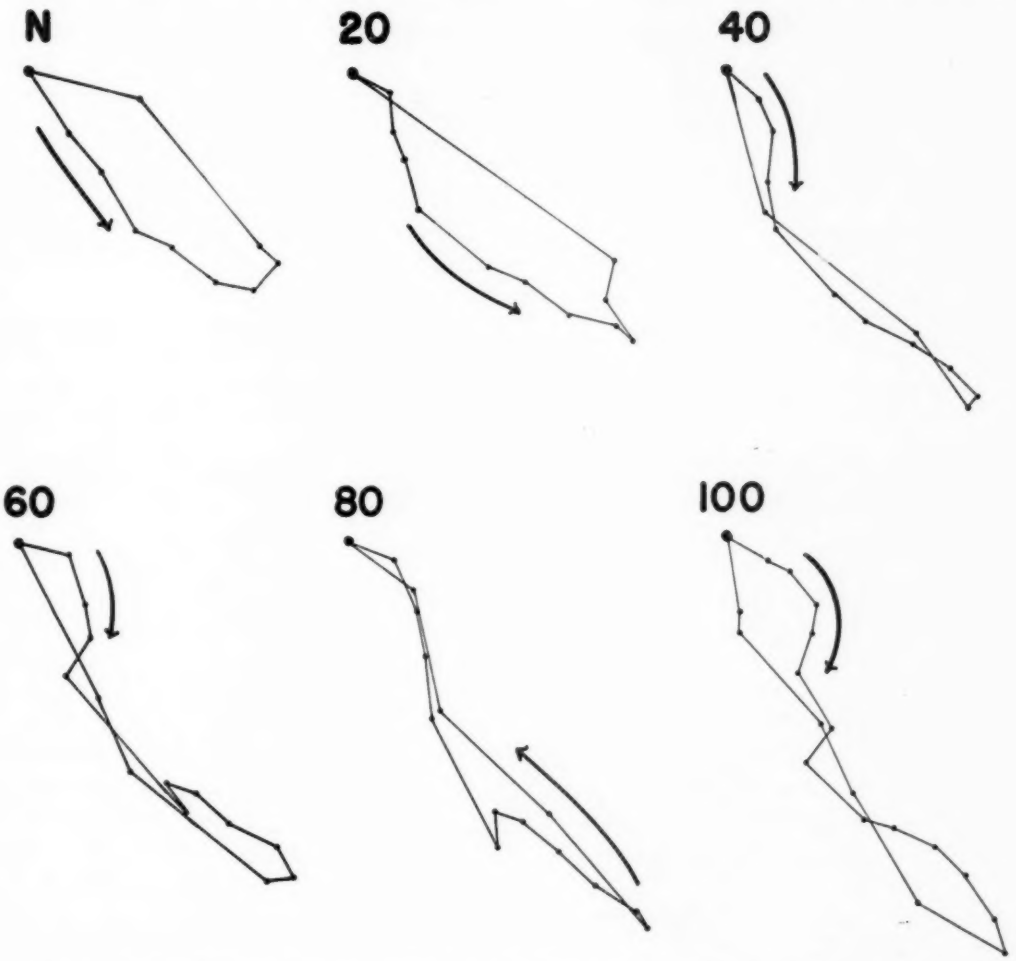


Fig. 1.—P loops derived from one atrial cast reflecting various degrees of right atrial enlargement. In this and succeeding figures the P loop or P wave derived from normal-sized atria is indicated by *N* and the per cent atrial enlargement is indicated by the numbers above the other P loops and waves.

enlargement studied. Increases in total duration of activation were not the same as apparent increases in the frontal plane loops since some of the activation process was perpendicular to this plane and because some of the activation lines appeared in this plane as closed circles. The increases in total and apparent duration are summarized in Table I.

No specific changes in the contour of frontal plane P loops were apparent. In general the loops tended to become narrower and more irregular with in-

creasing degrees of enlargement. Two loops derived from normal-sized atria were inscribed in a counterclockwise direction and one in a clockwise direction. With increasing right atrial enlargement these loops became more complex figures whose outlines crossed one or more times. One loop derived from normal-sized atria crossed itself twice and this form was maintained with the various degrees of right atrial enlargement studied.

The orientation of loops changed very little with right atrial enlargement. It is difficult to give a quantitative expression of the orientation of such figures, but in general the P loops derived from normal atria and from right atrial enlargement were located near plus 60 degrees in the frontal plane. P loops derived from one atrial cast with the various degrees of right atrial enlargement studied are shown in Fig. 1.

Since the orientation of P loops changed very little there were increases in the magnitude of P waves in essentially the same proportions as the increases in magnitude of vectors in the P loops. The increases in maximal amplitude of the P waves in Leads I and II are summarized in Table II.

TABLE II. CHANGES IN MAXIMAL AMPLITUDE OF P WAVES WITH ATRIAL ENLARGEMENT

DEGREE OF ENLARGEMENT	20%	40%	60%	80%	100%
Right atrial enlargement (Lead I)	8%	15%	18%	28%	29%
Right atrial enlargement (Lead II)	19%	37%	45%	54%	70%
Left atrial enlargement (Lead I)	21%	28%	43%	63%	73%
Left atrial enlargement (Lead II)	10%	16%	29%	25%	33%

The most consistent change in the form of P waves occurred in Lead II where the waves became high and peaked. This change is illustrated in Fig. 2. Waves in Lead II, derived from three of the atrial casts, had smooth contours with all degrees of enlargement studied. One cast yielded P waves which were high and peaked but in which notches on the ascending limb were present in those derived from 60 and 80 per cent degrees of right atrial enlargement. With

TABLE III. VCG CHANGES WITH LEFT ATRIAL ENLARGEMENT

DEGREE OF ENLARGEMENT (%)	INCREASE IN LENGTH OF AVERAGE MAXIMAL VECTOR (%)	AVERAGE INCREASE IN TOTAL DURATION (%)	AVERAGE INCREASE IN APPARENT DURATION (%)
20	13	11	20
40	19	24	36
60	34	33	45
80	37	41	56
100	44	52	69

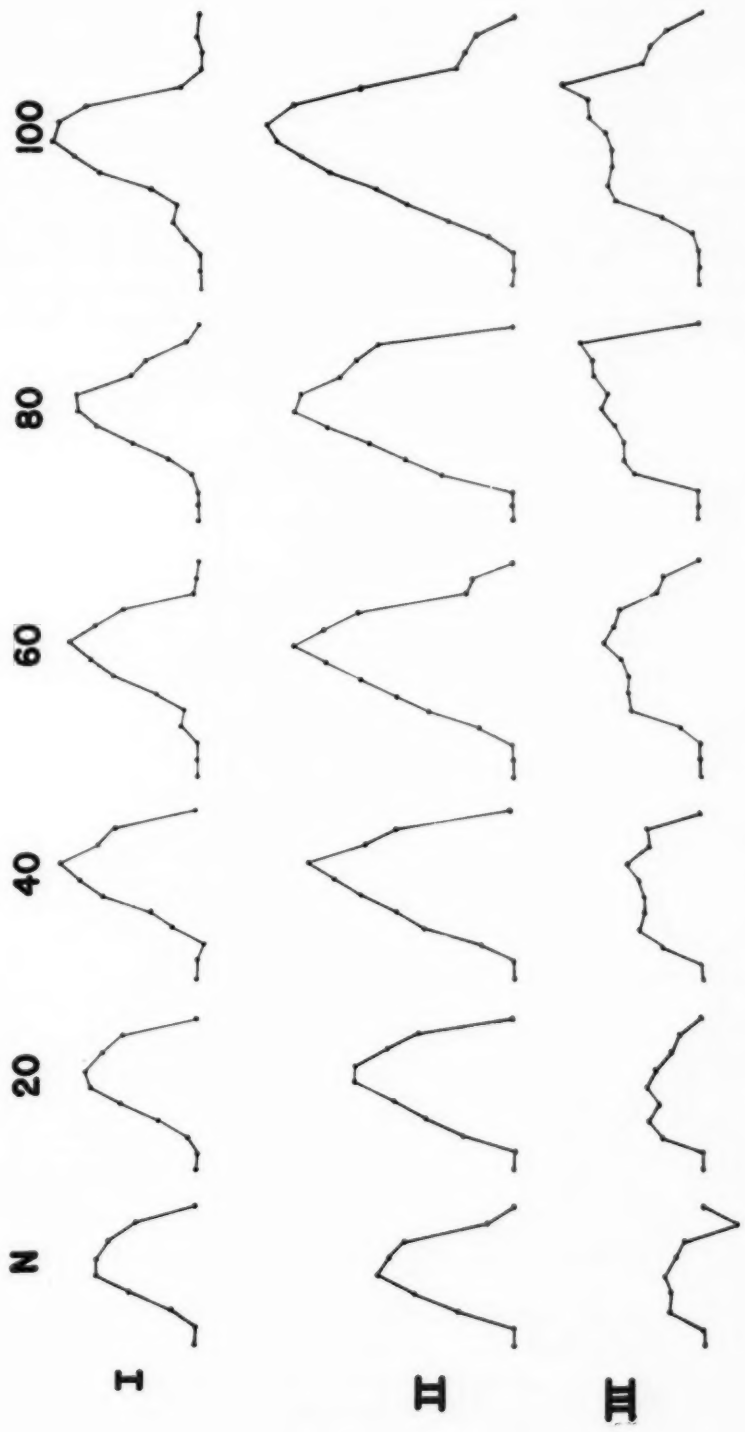


Fig. 2.—P waves derived from one atrial cast reflecting various degrees of right atrial enlargement.

100 per cent enlargement this notch was not present. The same cast yielded notched P waves in Lead I with 60 per cent and greater degrees of enlargement of the right atrium. P waves in Lead I derived from one other cast were notched on the ascending limb with all degrees of enlargement studied. In Lead III the P waves showed increased amplitude with right atrial enlargement but there were no consistent changes in form.

Left Atrial Enlargement.—There was less increase in length of vectors with left atrial enlargement than occurred with comparable degrees of enlargement of the right atrium. There was also less increase in total and apparent duration of atrial activation with left atrial enlargement. The average increases in length and in total and apparent duration are summarized in Table III.

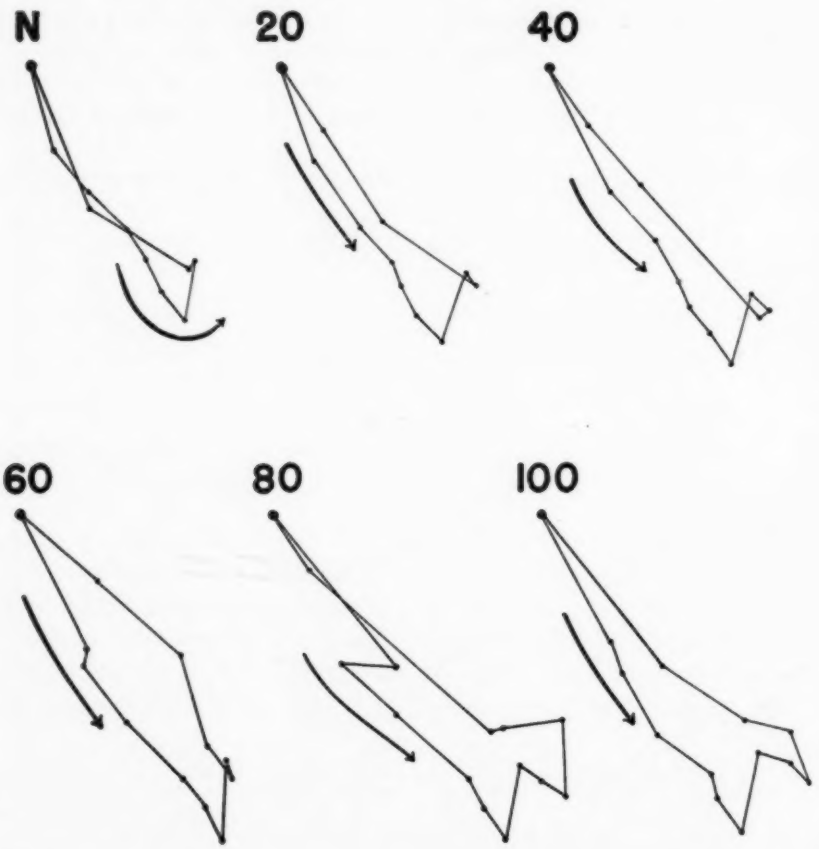


Fig. 3.—P loops derived from an atrial cast reflecting various degrees of left atrial enlargement.

With increasing left atrial enlargement the P loops became more open figures. Loops derived from the cast which yielded a clockwise loop with no atrial enlargement gave a twisted loop with 20 per cent left atrial enlargement and all greater degrees of enlargement yielded loops inscribed in a counterclockwise direction. The other atrial casts gave P loops inscribed in a counterclockwise direction with all degrees of left atrial enlargement studied. Three of the casts gave P loops which became increasingly irregular as the degree of

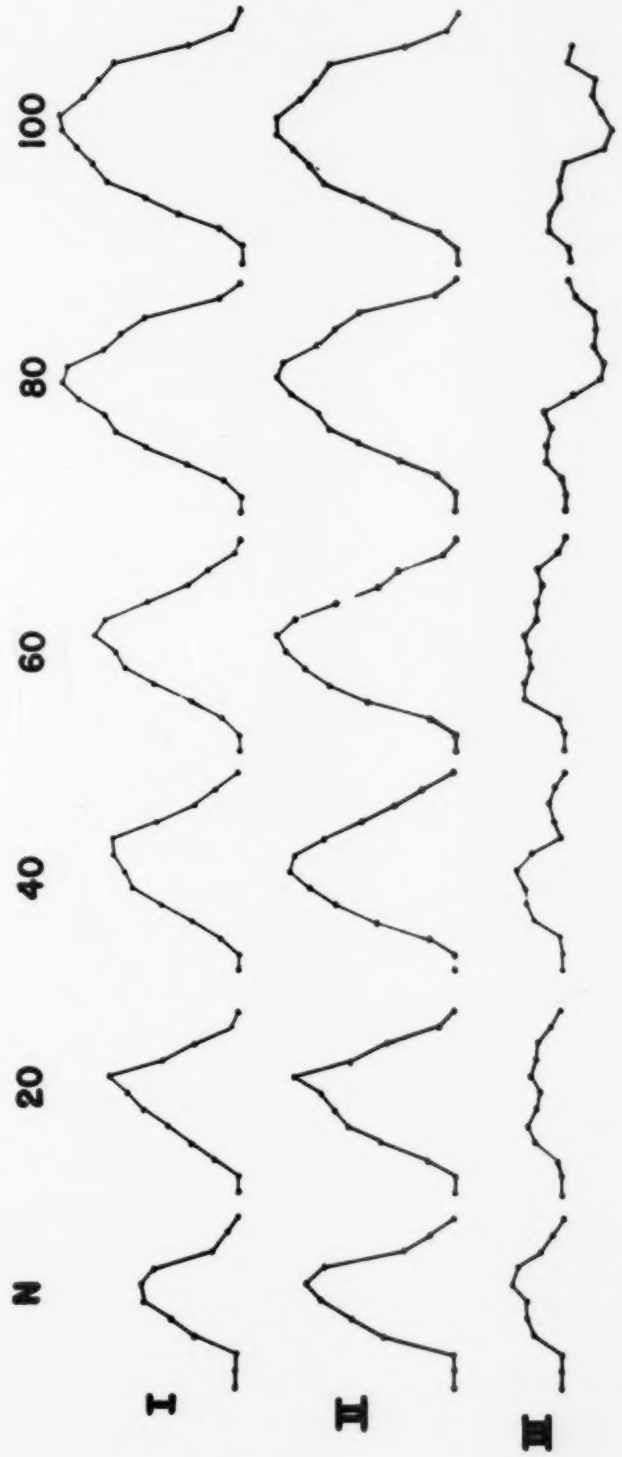


Fig. 4.—P waves derived from an atrial cast reflecting various degrees of left atrial enlargement.

enlargement increased. These irregularities tended to occur in the midportions of the loops and were considerably more marked than those which occurred with right atrial enlargement. The other cast yielded smooth P loops with all degrees of enlargement studied but these contained several vectors of approximately equal magnitude.

Unlike loops derived from right atrial enlargement, these loops showed a definite and progressive change in orientation with increasing left atrial enlargement. As stated previously it is difficult to quantitate this finding, but it is partially reflected by the fact that the average maximal vector of the normal loops was located at plus 48 degrees, while that of the loops derived from 100 per cent enlargement of the left atrium was located at plus 35 degrees. P loops from one atrial cast reflecting the degrees of left atrial enlargement studied are shown in Fig. 3.

The major changes in contour of P waves with left atrial enlargement consisted of the development of notches and a tendency of the waves to become flat topped. All atrial models gave progressively more flat-topped waves with the increments of enlargement studied. This finding is illustrated in Fig. 4. One model gave notched waves in Lead I with 100 per cent enlargement of the atrium but not with lesser degrees of enlargement. The same model yielded a slightly notched P wave in Lead II with no atrial enlargement and this became progressively more marked with increasing size of the atrium. One model gave smooth waves with all degrees of enlargement studied. Another model yielded notched P waves in Lead I with 60 and 80 per cent enlargement and smooth P waves with 100 per cent enlargement of the left atrium. The other model yielded P waves in which notching appeared in Lead I with 60 and 80 per cent enlargement of the atrium.

Since there were significant changes in the orientation of P loops with left atrial enlargement the increase in magnitude of the P waves was not the same as that of derived vectors. The orientation of vectors shifted toward the patient's left so that the amplitude of P waves in Lead I increased more than that in Leads II and III. The changes in maximal amplitude of P waves in Leads I and II are summarized in Table II. As shown in that table the per cent increase in maximal amplitude of P waves in Lead I with left atrial enlargement was greater than that of P waves in Lead II with right atrial enlargement. In Lead II the increase in amplitude resulting from left atrial enlargement was much less than that which occurred with enlargement of the right atrium.

DISCUSSION

The limitations of the method of analysis employed in this study have been discussed in previous publications. These include the assumption that atrial activation begins at the point marking the junction of the superior vena cava and right atrium and spreads in a simple radial fashion. In deriving the P waves in this study it is also assumed that the limb electrodes define an equilateral triangle. An additional limitation of the method of analysis is that repolarization may be occurring simultaneously with the later portions of depolarization. In this study depolarization has been treated as a process isolated

in time from repolarization. Despite these limitations, the similarity of P waves derived by the method described and those actually recorded prior to the death of the patients from whom atrial casts were made seems to indicate that the method is reasonably accurate.

As anticipated from existing information, the major ECG findings with atrial enlargement were increased amplitude and a peaked contour of P waves in Lead II with right atrial enlargement and flat-topped or notched P waves in Lead I with enlargement of the left atrium. Several aspects of the quantitative data obtained in this study seem worthy of emphasis. The high peaked P waves which occurred with right atrial enlargement were the result of increased length of vectors in the frontal plane. There was little change in orientation of vectors with right atrial enlargement. With left atrial enlargement there was less increase in length, but fairly marked changes in orientation of vectors. The increased amplitude of P waves in Lead I with left atrial enlargement was largely the result of the altered orientation of vectors. The per cent increase of maximal P wave amplitude in Lead I with left atrial enlargement was comparable to that in Lead II with enlargement of the right atrium.

The changes in form of the P waves were of special interest since P-wave contour is currently employed clinically as an aid in recognizing atrial enlargement. As expected, right atrial enlargement resulted in high peaked waves in Lead II, but in two instances there was also notching of the waves in Lead I or Leads I and II with at least some of the degrees of enlargement studied. Left atrial enlargement did not always result in notching of the P waves. Two models yielded notched P waves with the intermediate degrees of enlargement studied and not with lesser or greater amounts of enlargement. One model gave notched P waves in Lead I only with 100 per cent left atrial enlargement and one model yielded smooth waves with all degrees of enlargement studied.

The P loops derived in this study are of interest since some of the evidences of atrial enlargement seemed more easily evident in these records than in the P waves. Right atrial enlargement resulted in increased magnitude of vectors but no marked changes in their orientation. There were no specific changes in contour of P loops with right atrial enlargement although they tended to become narrower and more irregular. Left atrial enlargement resulted in less increase in magnitude of vectors, but their orientation shifted progressively toward the left with increasing degrees of enlargement. The P loops became wider figures enclosing larger areas as the degree of enlargement increased. These findings suggest that the VCG may be helpful in recognizing atrial enlargement and are consistent with clinical reports of the VCG in atrial abnormalities.[3]

Whether the ECG or VCG is employed, these studies emphasize the necessity for more detailed recording of electrical events from the atria than are generally used. In adults the average P wave in Lead II has a maximal magnitude of approximately 0.1 mv.[4,5] In the ECG recorded by conventional methods this is represented by a deflection of 1 mm. Since it is difficult to recognize variations in either voltage or time represented by changes of less than 0.5 mm. on the ECG, the P wave must be increased in magnitude by 50 per cent to be

clearly recognized. In this study this degree of increased magnitude was only reached with 80 per cent and greater amounts of right atrial enlargement. The average duration of P waves is 0.09 second which is represented on the conventional ECG as 2.25 mm.[5] To be clearly identifiable the P-wave duration would have to be increased approximately 20 per cent. This amount of prolongation of activation apparent in the frontal plane was only reached with degrees of right or left atrial enlargement greater than 20 per cent.

SUMMARY

The ECG and VCG effects of various degrees of right and left atrial enlargement have been studied. The method employed consisted of derivation of P loops and P waves from casts of the interior of the atria of four normal hearts. Photographic enlargements of the models were employed to obtain the various degrees of atrial enlargement studied.

The major VCG effect of right atrial enlargement was increased length of vectors without marked changes in orientation. In the ECG these vectors of increased magnitude were reflected by increased amplitude of P waves in Lead II. Two atrial models yielded notched P waves in Lead I or Leads I and II with some of the degrees of right atrial enlargement studied.

Left atrial enlargement resulted in less increase in magnitude of vectors but there was a progressive shift in orientation of vectors toward the left. The P loops enclosed progressively greater areas with increasing left atrial enlargement. The P waves became flat topped or notched with left atrial enlargement, but in some instances notching of the waves occurred only with certain degrees of enlargement.

With comparable degrees of enlargement there were greater increases in duration of atrial activation with right than with left atrial enlargement. Neither the increases in duration of activation, length of frontal plane vectors, or amplitude of P waves were linear with the degrees of enlargement studied.

REFERENCES

1. Abildskov, J. A., Cronvich, J. A., and Burch, G. E.: Circulation **11**:97, 1955.
2. Abildskov, J. A., Barnes, T. G., and Hisey, B. L.: Am. Heart J. **52**:496, 1956.
3. Fowler, N. O., and Dorney, E. R.: Am. Heart J. **48**:36, 1954.
4. Kossmann, C. E.: Circulation **8**:920, 1953.
5. Lepeschkin, E.: Modern Electrocardiography, Vol. 1, Baltimore, 1951, Williams & Wilkins Company.

SIMULTANEOUS ESOPHAGEAL AND STANDARD ELECTROCARDIOGRAPHIC LEADS FOR THE STUDY OF CARDIAC ARRHYTHMIAS

ALBERT D. KISTIN, M.D.,* AND JAMES C. BRUCE, M.D.**

WASHINGTON, D. C.

THE value of esophageal electrocardiographic leads for the study of cardiac arrhythmias is well established and depends on the recording of large distinctive P waves which may be barely discernible or absent in other leads.[1-30,43,44] We have encountered two difficulties, however, in the use of esophageal leads alone: (1) It is sometimes impossible to distinguish P and QRS or to separate them when they are superimposed, because their component rapid deflections may be similar, and their relative sizes may vary widely, P being equal to, larger, or smaller than QRS; (2) Differences in configuration of QRS and even P may be more apparent in other leads. These difficulties become important in complex arrhythmias where events are rapidly and irregularly changing and where it is necessary to identify individual complexes. The use of a simultaneous standard lead obviates the difficulties, and we propose this as a useful method for practical diagnosis and theoretical study.

Previous studies of arrhythmias with simultaneous esophageal and standard leads emphasize the limitations of the standard leads,[3,8,25-28,44] or are concerned with the physiology of atrial arrhythmias, the diagnosis of which is simple, rather than with the unraveling of complex arrhythmias.[14,18,22,26] Luisada[2] proposed the simultaneous use of a bipolar esophageal lead and a tongue-xiphoid lead for the study of left and right atrial activity, respectively, and this method was used by others.[4-6,9] The present study demonstrates the complementary value of simultaneous esophageal and standard leads in elucidating some complex atrial and ventricular arrhythmias. In our opinion Figs. 10, 11, 15, and 16 of the study by Calvino and associates[44] demonstrate this also.

The esophageal electrode was one of several German silver rings on a multiple-electrode Nyboer-tube. V-esophageal leads were obtained from levels that by trial yielded optimum, large P waves. The simultaneous standard leads were usually Lead II and/or V_1 or V_2. The Technicon direct-writing three-channel electrocardiograph was used, and the tracings were recorded at a paper speed of 25 mm. per second. The photographs are of unretouched tracings.

From the Department of Medicine, The District of Columbia General Hospital and The George Washington University School of Medicine, Washington, D. C.

Supported in part by a grant from the National Heart Institute, National Institutes of Health, Bethesda, Md.

Received for publication Feb. 28, 1956.

*Assistant Clinical Professor of Medicine, The George Washington University School of Medicine, Washington, D. C.; Chief of Medicine, Beckley Memorial Hospital, Beckley, W. Va.

**Former Fellow in Cardiology, The District of Columbia General Hospital and The George Washington University School of Medicine.

The esophageal leads are designated in the illustrations as *E* followed by a number indicating the location of the electrode in centimeters from the nares.

CASE 1 (FIG. 1).—*Atrial tachycardia (flutter) with multifocal ventricular ectopic systoles or variations in ventricular conduction:* P waves were not discernible in any of the standard leads, of which II and V_1 are shown. The simultaneous E lead shows large regular P waves at a rate of 300 per minute. The variations in QRS configuration, obvious at a glance in II and V_1, are impossible to determine in E36. The varying distortion of P by QRS in the E lead is not necessarily evidence of varying configuration of QRS, since it occurs also when similar QRS complexes fall at slightly different times with relation to P. The latter occurs here with the first, second, fifth, and seventh QRS complexes.

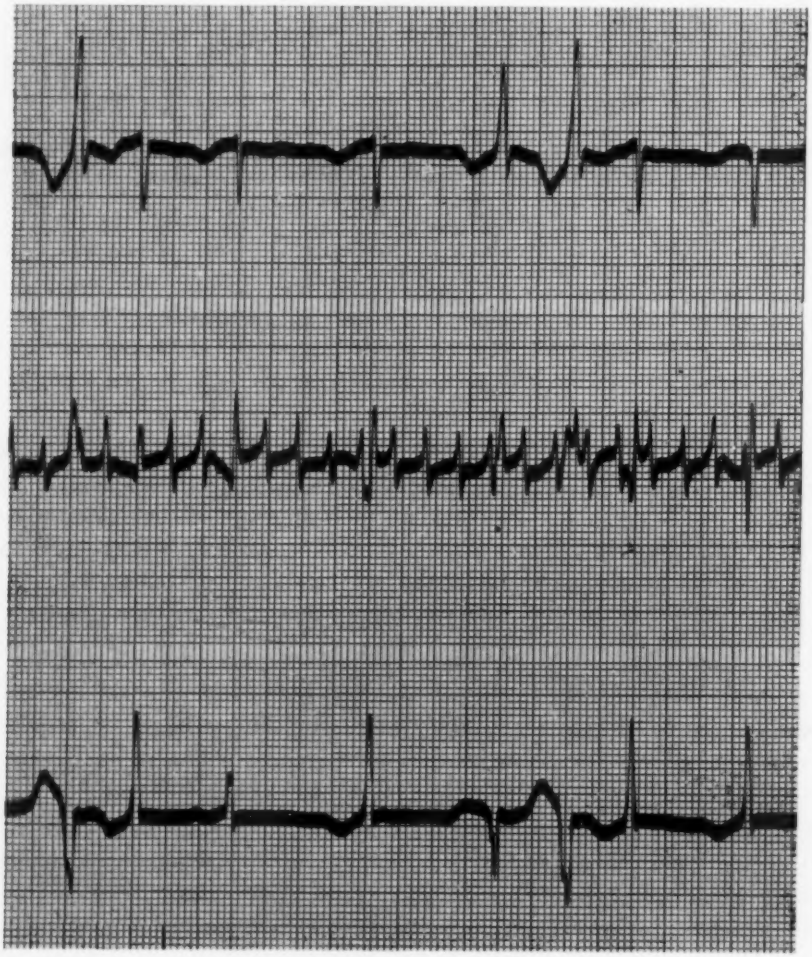


Fig. 1.—(Case 1) Atrial tachycardia (flutter) with multifocal ventricular ectopic systoles or variations in ventricular conduction.

CASE 2 (FIG. 2).—*A-V dissociation with interference, two atrial foci discernible only in the E lead, two types of QRS discernible only in Lead III:* The interpretation here is A-V dissociation with interference, the R-R intervals of the ventricular pacemaker being represented in the last four QRS complexes of the lower strip, and the much slower P-P interval of the atrial pacemaker being represented by the first two P waves of both strips. The second and fourth QRS complexes of both strips are considered to be conducted interference beats. In portions of the tracing not shown here the diagnosis of A-V dissociation with interference is obvious and uncomplicated. In

Lead III here, however, this interpretation becomes confused by the shorter interval in the upper strip between the second and third P waves which seem similar, and by the absence of P in the last part of the lower strip, the latter being unexplained by possible superimposition of P on QRS. The explanation is in the esophageal lead which shows that the third P wave is from another focus and this P wave occurs again following the fifth QRS of the lower strip and probably superimposed on the last QRS of the upper strip and on next to the last QRS of the lower strip. There are at least two configurations of QRS in Lead III which seem to alternate as if the intraventricular conduction varies from beat to beat. This variation of QRS is not discernible in the E lead.

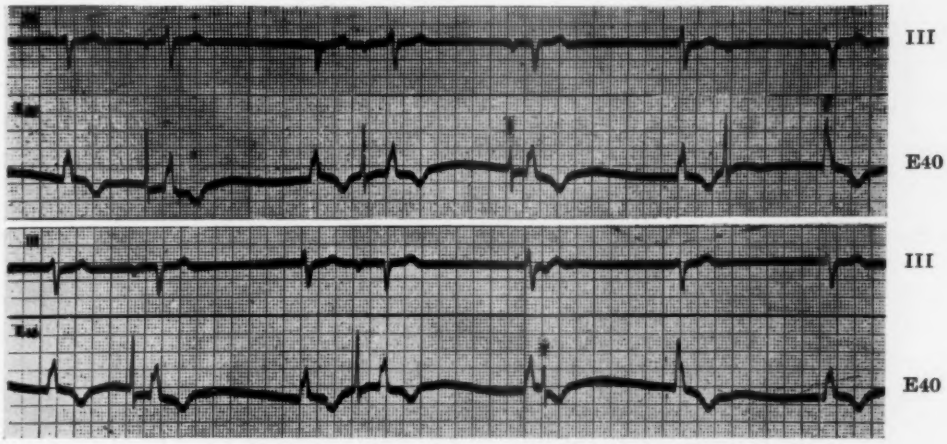


Fig. 2.—(Case 2) A-V dissociation with interference, different atrial foci discernible only in the E lead, different QRS complexes discernible only in Lead III.

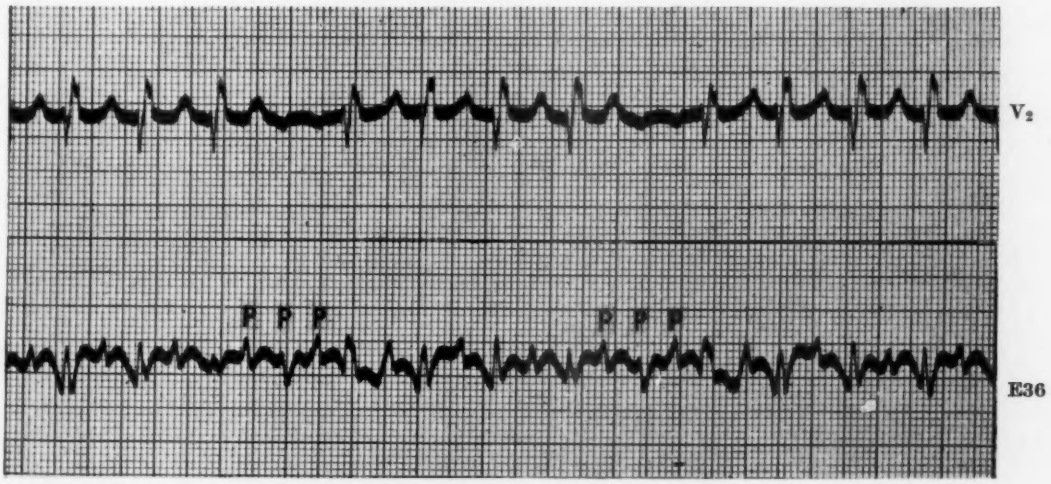
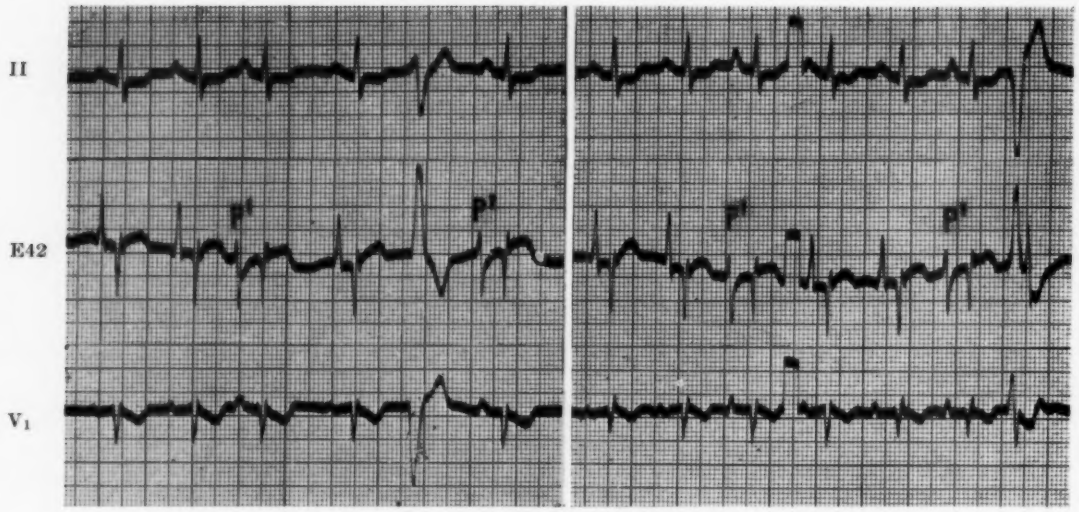


Fig. 3.—(Case 3) Atrial tachycardia (flutter) with alternating bidirectional P waves and variable A-V block.

CASE 3 (FIG. 3).—*Atrial tachycardia (flutter) with alternating bidirectional P waves and varying A-V block:* The diagnosis of atrial tachycardia (flutter) becomes apparent in V_1 during the two intervals of increased A-V block when small inverted P waves appear. The simultaneous E lead shows during these two gaps between ventricular complexes three P waves; alternate P waves differ in configuration and in this E lead are opposite in direction. Alternate differences in configuration of P are present at two esophageal levels in addition to the one illustrated, although the P waves at these levels differ from those of E36. This supports the interpretation and elimi-



A. *B.*

Fig. 4.—(Case 4) Atrial parasystole, differences in atrial foci apparent in the standard leads but not in the E lead.

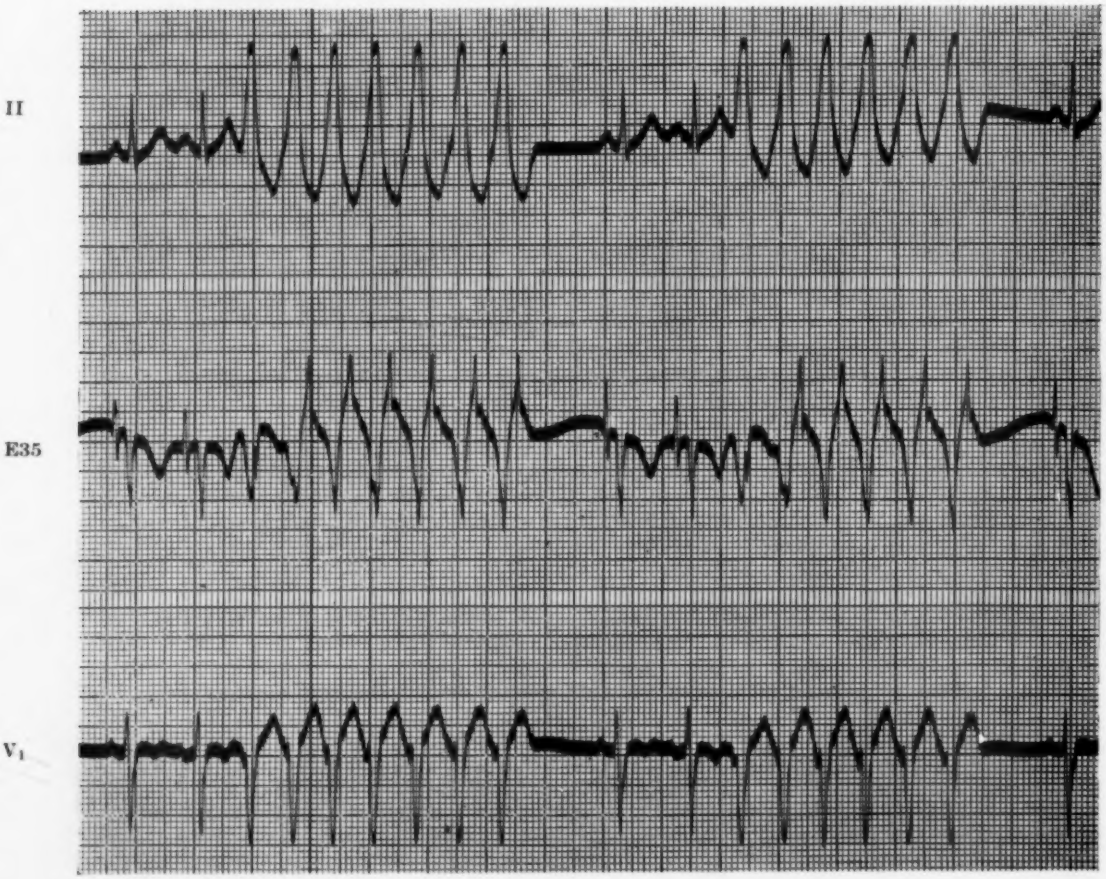


Fig. 5.—(Case 5) Ventricular tachycardia with retrograde conduction to the atria.

nates the possibility of some peculiar artefact. This diagnosis is impossible in either lead alone. The E lead alone is confusing; even if the atrial tachycardia were recognized here, the varying distortions would be attributed to varying superimposition of QRS complexes. One possible explanation is sinus or atrial tachycardia at a rate of about 136 with coupled atrial bigeminy. Another possible explanation is atrial tachycardia (or flutter) at a rate of about 272 with alternating variation in atrial spread of the impulse.

CASE 4 (FIG. 4).—*Atrial parasystole, different atrial foci apparent in the standard leads, but not in the E lead:* The configurations of the premature P waves (P′) in both parts (*A* and *B*) of the tracing are similar in the E lead but the simultaneous standard leads indicate that the premature atrial beats in *A* differ in origin from those in *B*. The following measurements support this interpretation. There are fifteen P′-P′ intervals of atrial premature systoles whose standard lead configuration is that illustrated in *A*. Fourteen of these intervals are in the range 2.01 to 2.16 sec., and the P-P′ times vary from 0.44 to 0.56 sec. The possibility of atrial parasystole is considered. There are eight P′-P′ intervals of atrial premature systoles whose standard lead configuration is that illustrated in *B* or differs from both *A* and *B*, or one atrial premature systole is of one type and the second of another. None of these eight intervals is in the range 2.01 to 2.16 sec., nor a simple whole number multiple or dividend thereof.

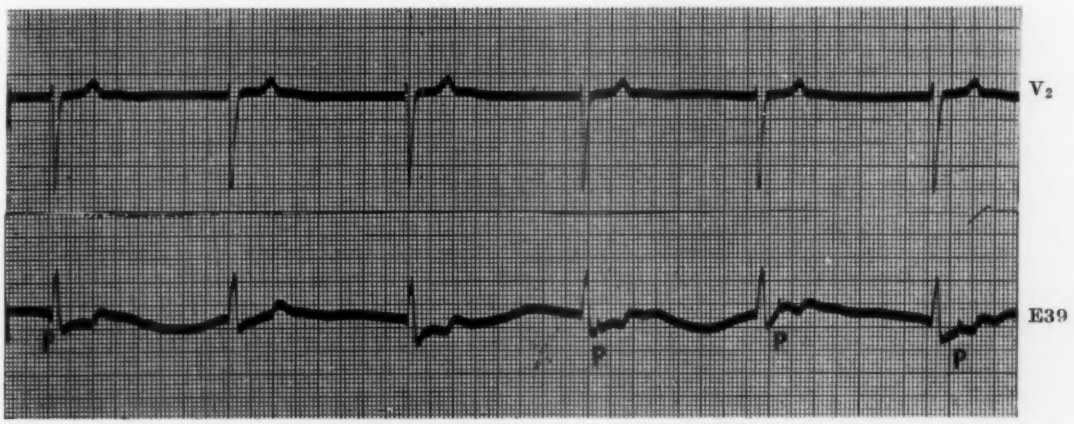


Fig. 6.—(Case 6) A-V dissociation.

CASE 5 (FIG. 5).—*Ventricular tachycardia with retrograde conduction to the atria:* This electrocardiogram has previously been described.[25] There are two runs of ventricular tachycardia. In the E lead superimposed on the first QRS of each run is the regular sinus P wave, whereas each subsequent QRS is followed by a P wave produced by retrograde conduction to the atria. The simultaneous standard leads support this interpretation in that the configuration of the first and subsequent QRS complexes of each run are similar in Leads II and V_1; in the E lead alone the retrograde P wave might possibly be considered part of the QRS and some other explanation might be sought for the difference between the first and subsequent QRS complexes of each run.

CASE 6 (FIGS. 6 and 7).—*Double reciprocal beats (return extrasystoles) after ventricular ectopic systoles:* The basic rhythm here is A-V dissociation (Fig. 6), the P-P cycles being slightly longer than the R-R cycles. The P waves are visible in the E lead, the first preceding QRS, the second and third superimposed on QRS, and the last three following QRS. There are ventricular ectopic systoles from at least five different foci, three of which, X_1, X_2, and X_3, are illustrated in Fig. 7. All ventricular ectopic systoles are followed by retrograde conduction to the atria[25] unless they occur soon after or at about the same time as the atrial systole of the basic atrial rhythm. The retrograde ventriculoatrial conduction time varies, and when it is sufficiently long (X_2) the ectopic systole is followed by a group of four complexes (P_1, R_1, P_2, and R_2), R_1 and R_2 resembling the QRS of the basic idioventricular or nodal rhythm. This group of four complexes occurs nineteen times after three of the ectopic systoles and at no other time in practically continuous electro-

cardiograms covering a period of about twenty-one recorded minutes. The interpretation is: P_1 = retrograde atrial activity following X, R_1 = reciprocal beat (return extrasystole), P_2 = retrograde atrial activity from R_1, and R_2 = second reciprocal beat following P_2. The difference between P_1 and P_2 may be explained by different spread of the retrograde impulse because of refractory fibers and because P_2 follows relatively soon after P_1. Lead II was not obtained simultaneously with the E lead in this case, but the constellation of beats shown in Fig. 7 was observed in Lead II at other times, and magnified tracings show small inverted waves where P_1 and P_2 would be expected.

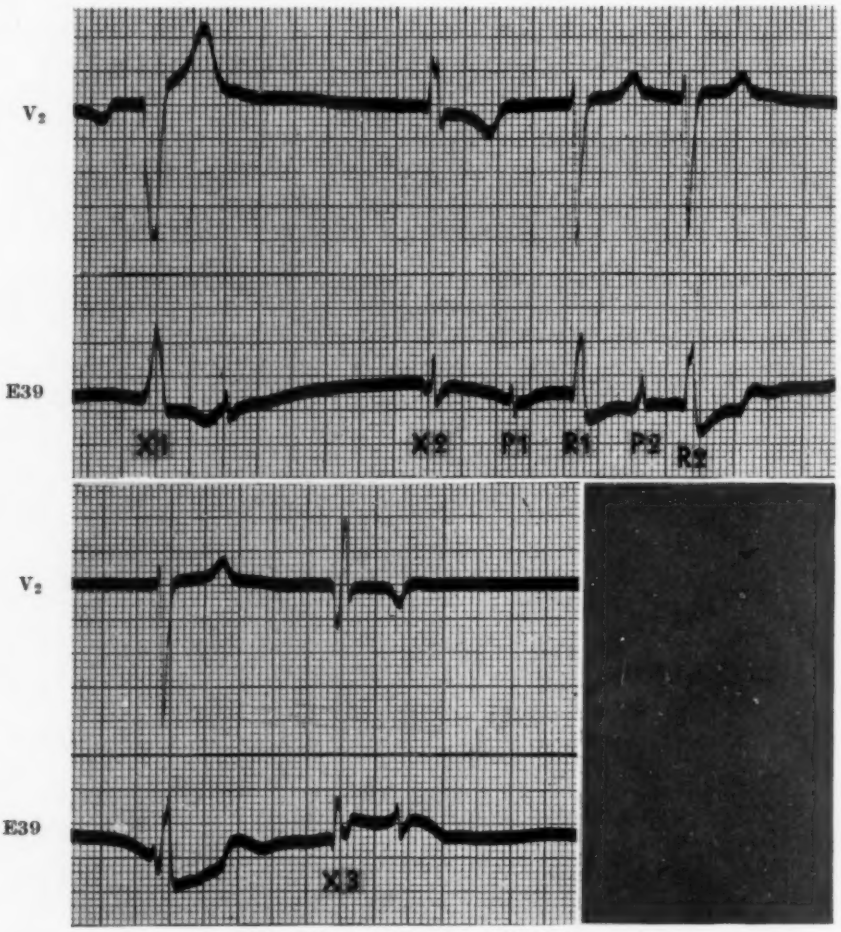


Fig. 7.—(Case 6) Retrograde conduction from ventricular ectopic systoles. Double reciprocal beats after ventricular ectopic systole.

Detailed analysis of a large amount of data supports the interpretation. R_1-P_2 and P_2-R_2 are constant within a narrow range regardless of which X focus initiates the cycles. Comparable values of X-P_1 and P_1-R_1 occur after all three X foci; variations in these values are explained by (1) two pathways of retrograde (V-A) conduction,[25] (2) difference in site of origin of X, and (3) occurrence of X and P_1 in or out of a supernormal phase.

While the interpretation depends largely on the esophageal lead, the value of the simultaneous standard lead is illustrated in Fig. 7. This lead gives assurance that P_1 and P_2 are correctly designated and are not QRS complexes. Furthermore in the measurements it is important to identify the different ectopic foci; in the E lead there might be some question whether X_2 and X_3 are from the same ectopic focus, but the simultaneous V_2 shows clearly that they are not.

DISCUSSION

Complex as cardiac arrhythmias and the physiologic concepts underlying them may be, the electrocardiographic data available for their analyses are relatively simple, consisting of (1) temporal relations between P and QRS and (2) configurations of P and QRS from which deductions are made regarding origin of impulse and mode of spread of impulse. While QRS is usually large and distinct in most leads, under certain circumstances atrial activity may give rise to barely perceptible or even no recognizable P in the electrocardiographic leads usually used. Various leads have been proposed to record atrial activity better, but the esophageal lead is probably best, taking into consideration simplicity, reliability, and size and distinctiveness of the P waves obtained. If the tube is passed with patience and gentleness, the esophageal lead may be obtained in most patients with little discomfort, although occasionally in seriously ill patients the discomfort must be weighed against the value of the information sought. Because of the size of the esophageal P wave and because it may resemble QRS, difficulties are sometimes presented which are obviated if a simultaneous standard lead is used. This is amply illustrated in the described electrocardiograms.

If the electrocardiogram is considered in relation to the three-dimensional electrical field of the heart it is not surprising that two simultaneous leads will sometimes give a better picture than one of P or QRS configuration. Different spatial electrical fields may conceivably be so related to a single lead as to produce similar effects in the lead, but are less apt to do so in two independent leads. This applies to Cases 2 and 4. In the former the E lead permits recognition of different P configuration not apparent in Lead III, whereas the difference in QRS configuration is apparent in Lead III but not in the E lead. In Case 4, P configurations which seem similar in the E lead are revealed to be different in Leads II and V_1. If the esophageal P wave, instead of being regarded from a vector or spatial point of view,[35] is believed to be a semidirect lead with an intrinsic deflection[3,36] it is still conceivable with respect to Case 4 that different foci might fortuitously be equidistant from and similarly situated with respect to the esophageal electrode so as to produce similar P waves. If the problem of distinguishing different atrial foci is recognized at the time of recording the arrhythmia it may be solved also by recording E leads at different levels.

The lead combination of Luisada[2] would probably be useful in the analyses of at least some of the arrhythmias described here, even though it was used for a different purpose. The bipolar E lead of Luisada may record little or no QRS, although sometimes QRS is large. The small or absent QRS might be an advantage in some instances in that the P waves would not be obscured, but it might be a disadvantage in other instances because there would be only one lead for evaluation of QRS configuration. An adequate comparative study of the bipolar E lead of Luisada and the V-E lead from the point of view of utility for the study of arrhythmias has not been made. The claim of Luisada[2,12] and others[4-6,9] that it is possible to record separately "left atrial" and "right atrial" activity by their method is not proved. Tracings similar to that of Case 1 of this study were interpreted by these authors as showing fibrillation of the right

atrium and flutter of the left. Another possible explanation is that the spatial electrical field is so oriented as to produce little deflections in one lead and large deflections in the other without any relation to difference in activity of the two atria.

It is a commentary on the value of the method described here that it has revealed such unusual conditions as those of Cases 3 and 6. We are aware of no previous reports that resemble Case 3. We do not believe this is related to the reported cases of double atrial rhythm.[37,38] In those cases the two atrial rhythms are relatively slow and apparently unrelated to each other in time so that the two types of P waves occur at irregular intervals. In Case 3 the two types of P waves alternate in a constant temporal relation and the atrial rate is rapid. Reciprocal beats from ventricular premature systoles as illustrated in Case 6 have been reported only rarely[25,31-34,39-42,45] and double reciprocal beats only once.[32] It may be that the conditions represented in Cases 3 and 6 are indeed rare, but we believe that they and other complex arrhythmias will be recognized more frequently and be more amenable to analysis by the described method, contributing to the understanding of the mechanisms of arrhythmias.

SUMMARY

The value of esophageal leads for the study of cardiac arrhythmias is well established, but we found difficulties in some cases; (1) It may be impossible to distinguish P and QRS or to separate them when they are superimposed, because their component rapid deflections may be similar, and their relative sizes may vary widely, P being equal to, larger, or smaller than QRS; and (2) Differences in configuration of QRS and even P may be more apparent in other leads. These difficulties may be obviated by the use of a simultaneous standard lead. The complementary value of simultaneous standard and esophageal leads is illustrated in six cases: (1) atrial tachycardia (flutter) with multifocal ventricular ectopic systoles or variations in ventricular conduction; (2) A-V dissociation with interference, different atrial foci discernible only in the E lead, and different QRS complexes discernible only in Lead III; (3) atrial tachycardia (flutter) with alternating bidirectional P waves; (4) atrial parasystole, difference in atrial foci apparent in the standard leads, but not in the E lead; (5) ventricular tachycardia with retrograde conduction to the atria; and (6) double reciprocal beats (return extrasystoles) after ventricular ectopic systoles. The arrhythmia of Case 3 has not previously been described and that of Case 6 only once. Their recognition is an indication of the value of the method.

REFERENCES

1. Baur, L.: Deutsch. Arch. klin. Med. **145**:129, 1924.
2. Luisada, A.: Cuore e circolag. **19**:77, 1935.
3. Brown, W. H.: Am. Heart J. **12**:1, 306, 1936.
4. Rubino, A.: Clin. med. ital. **67**:168, 1936.
5. Rubino, A.: Cuore e circolag. **20**:57, 1936.
6. Laufer, S., and Rubino, A.: Clin. med. ital. **67**:363, 1936.
7. Tacquini, A. C.: Exploracion del corazon por via esofagica, Buenos Aires, 1936, El Ateneo.
8. Harvey, A. McG.: Ann. Int. Med. **11**:57, 1937.
9. Sossai, A.: Cuore e circolag. **22**:441, 1938.

10. Deglaude, L., and Laubry, P.: Arch. mal coeur. **32**:121, 1939.
11. Nyboer, J., and Hamilton, J. G. M.: Brit. Heart J. **2**:263, 1940.
12. Luisada, A.: J. Lab. & Clin. Med. **25**:1146, 1940.
13. Wuensche, H. W.: Deutsch. Arch. klin. Med. **186**:358, 1940.
14. Kossmann, C. E., and Berger, A. R.: Ann. Int. Med. **15**:128, 1941.
15. Butterworth, S., and Poindexter, C. A.: Am. Heart J. **32**:681, 1946.
16. Frau, G.: Folia cardiol. **5**:173, 1946.
17. Schlesinger, P., and Moraes, J. de: Arq. clin. **5**:183, 1947.
18. Cabrera Cosio, E., and Sodi-Pallares, D.: Arch. Inst. cardiol. México **17**:850, 1947.
19. Schwartz, M.: Northwest Med. **46**:448, 1947.
20. Wenger, R.: Cardiologia **13**:284, 1948.
21. Levine, H. D., Hellems, H. K., Wittenberg, M. H., and Dexter, L.: Am. Heart J. **37**:46, 1949.
22. Franke, H.: Ztschr. klin. Med. **146**:171, 1950.
23. Foster, R. F., and Thayer, R. H.: Am. Heart J. **40**:224, 1950.
24. Enselberg, C. D.: Am. Heart J. **41**:382, 1951.
25. Kistin, A. D., and Landowne, M.: Circulation **3**:738, 1951.
26. Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R. W., and Kruger, H. E.: The Auricular Arrhythmias, Springfield, Ill., 1952, Charles C Thomas, Publisher.
27. Steinberg, M. F., Kroop, I. G., and Grishman, A.: J. Mt. Sinai Hosp. **18**:337, 1952.
28. Bellet, S.: Clinical Disorders of the Heart Beat, Philadelphia, 1953, Lea & Febiger.
29. Gregorczyk, K.: Przeglad Lekarski, Krakow **9**:310, 1953.
30. Bussan, R., Torin, S., and Scherf, D.: Am. J. M. Sc. **230**:293, 1955.
31. Malinow, M. R., and Langendorf, R.: Am. Heart J. **35**:448, 1948.
32. Grau, S., and Gouaux, J. L.: Circulation **2**:422, 1950.
33. Scherf, D., and Schott, A.: Extrasystoles and Allied Arrhythmias, Melbourne, 1953, William Heinemann.
34. Pick, A.: Circulation **8**:243, 1953.
35. Duchosal, P. W., and Grosgurin, J. R.: Circulation **5**:237, 1952.
36. Lewis, T., Meakins, J., and White, P. D.: Phil. Tr. Lond. s.B. **205**:375, 1914.
37. Geraudel, E.: Arch. mal coeur. **28**:121, 1935.
38. Scherf, D.: New England J. Med. **252**:928, 1955.
39. Levin, E.: Rev. argent. cardiol. **8**:197, 1941.
40. Langendorf, R., Katz, L. N., and Simon, A. J.: Brit. Heart J. **6**:13, 1944.
41. de Mesquito, Q. H.: Arq. brasil cardiol. **3**:275, 1950.
42. Schott, A.: Proc. Roy. Soc. Med. **44**:151, 1951.
43. Schrire, V., and Vogelpoel, L.: Am. Heart J. **49**:162, 1955.
44. Calvino, Jose M., Cano, Luis A., and Castellanos, A., Jr.: Rev. cubana cardiol. **16**:293, 1955.
45. Katz, L. N., and Pick, A.: Clinical Electrocardiography. Part I. The Arrhythmias, Fig. 61, Philadelphia, 1956, Lea & Febiger.

A STUDY OF THE INFLUENCE UPON THE SPATIAL VECTORCARDIOGRAM OF LOCALIZED DESTRUCTION OF THE MYOCARDIUM OF DOG

L. G. HORAN, M.D.,* G. E. BURCH, M.D.,** AND J. A. CRONVICH, M.S.***

NEW ORLEANS, LA.

RECENT interest concerning changes in the late and terminal portions of the QRSsÊ loop of the spatial vectorcardiogram (sVCG) and the QRS complex of the electrocardiogram (ECG) produced by myocardial infarction and damage[1,2] prompted these experiments in dogs. Studies in man have suggested that infarction in those portions of the myocardium that are depolarized late produces readily identifiable changes in the sVCG but less noticeable changes in the conventionally recorded electrocardiogram.[1,2] Changes are to be expected on the basis of current concepts in electrocardiography. If such concepts are valid, the sVCG and the ECG recorded at higher paper speed may conceivably reveal infarcts located in areas of the heart that are expected to alter only the later portions of these complexes and not the initial portions of the QRS complex or early portions of the QRSsÊ loop. Various selected areas of the heart of the dog were injured or destroyed while the ECG and the sVCG were being recorded in order to study further the relation of the anatomic site to the electrical activity of the cardiac muscle.

MATERIALS AND METHOD

Twenty-seven mongrel dogs were anesthetized with intravenous pentobarbital sodium (30 mg. per kilogram body weight), intubated with a tracheal cannula under direct laryngoscopy, and were then placed on a standard animal operating table. Two sets of electrodes were attached to the dog, one for recording the electrocardiogram and the other for the vectorcardiogram. The Wilson tetrahedral reference frame was employed for the vectorcardiogram, with the use of a subcutaneous back electrode placed 2 cm. to the left of the spinous process of the seventh dorsal vertebra. Control recordings were made of the sVCG and the standard ECG, including the V_1 to V_6 precordial leads obtained at the level of the fourth and fifth intercostal spaces before the chest was opened and again after it was temporarily closed prior to production of experimental injury. During the open-chest period, the lungs were inflated with oxygen administered through a respirator.†

Sites in the myocardium were destroyed in fifteen dogs by burning an area with a heated soldering iron, acetylene torch, or electric cautery; in five other dogs infarction was produced by ligation of one or more branches of the left coronary artery; and in seven additional dogs 25 to 50

Aided by a grant from the Public Health Service (H-143).

Received for publication Aug. 7, 1956.

*Public Health Service National Heart Institute trainee in cardiovascular diseases, Department of Medicine, Tulane University School of Medicine, New Orleans, La.

**From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana at New Orleans.

***From the School of Electrical Engineering, Tulane University, New Orleans, La.

†Pneophore Respirator, Mine Safety Appliance Co., Tulsa, Okla.

c.c. of formaldehyde was injected into the pericardial cavity. Two dogs died after the chest was opened but before any myocardial injury was inflicted, one of cardiac standstill and the other of dilatation and standstill following a period of slow, irregular idioventricular rhythm.

In all experiments, tracings were obtained before the lesion was inflicted, first with the chest open and then with it closed. Before formaldehyde was instilled into the pericardium, polyethylene catheters were tied in place (one leading to the pericardial cavity and the other to the thoracic cavity), the chest was closed, and entrapped air was evacuated from the pleural space by a syringe connected to the end of the polyethylene catheter brought out through the anterior thoracic wall. Continuous electrocardiographic recordings were made throughout the period of instillation and until the heart ceased to beat, an interval that did not exceed thirty minutes. As many vectorcardiograms as possible were obtained. In all experiments the hearts were removed and the extent and locations of the cardiac lesions were studied grossly by direct inspection and by manual drawings and photographs. Histologic sections of selected areas were obtained for microscopic study of the injury produced.

RESULTS

General Observations.—When the chest was opened and the heart was exposed to the room atmosphere, fairly characteristic changes were noted in the sVCG (Fig. 1). The mechanism for the changes was not clear but was probably partially attributable to alterations in the electrical field surrounding the heart consequent to its displacement during the surgical procedure. In addition, there may have been reflex phenomena that modified the coronary circulation, which, in turn, influenced the electrical behavior of the heart. Such a surgical procedure is traumatizing and abnormal for the animal in many ways other than hemodynamically, including biochemical, hormonal, and general metabolic factors that influence the myocardial physicochemical state. Mere cooling of the heart by the room air must have had some influence upon the bioelectric phenomena of the myocardium, but thermal influences were probably not solely responsible for the changes noted. Although the alterations produced in the sVCG were subtle in comparison with other changes observed during the course of these experiments, they were definite, consistent, and more readily detected when serially recorded sVCG's were compared. The changes produced by the surgical procedure and opening of the chest were decidedly different from those produced by injury and destruction to the myocardium, as described and discussed hereinafter.

Burns of the Left Ventricle.—In one of the twelve dogs in which the subepicardial area of the left ventricle was burned, ventricular tachycardia and fibrillation developed the moment the electrocautery was applied to the heart, and in three the sVCG showed no significant changes other than those usually produced by opening of the chest (Fig. 1). In the remaining eight, alterations occurred that were predictable from present-day electrocardiographic theory. The changes are summarized in Fig. 2.

In general, there were always definite, but surprisingly minor, changes. The QRSsÊ loop was deformed in essentially the mid-portion in time (Fig. 1) but not in the initial portion except in one instance when a large coronary artery (anterior descending branch of the left coronary artery) was burned. In this case, the main change was a reduction in magnitude of the vectors (Dog No. 512). The minor alterations in magnitude and configuration of the QRSsÊ loop were also evident in the electrocardiogram. The S-T segmental portions of the

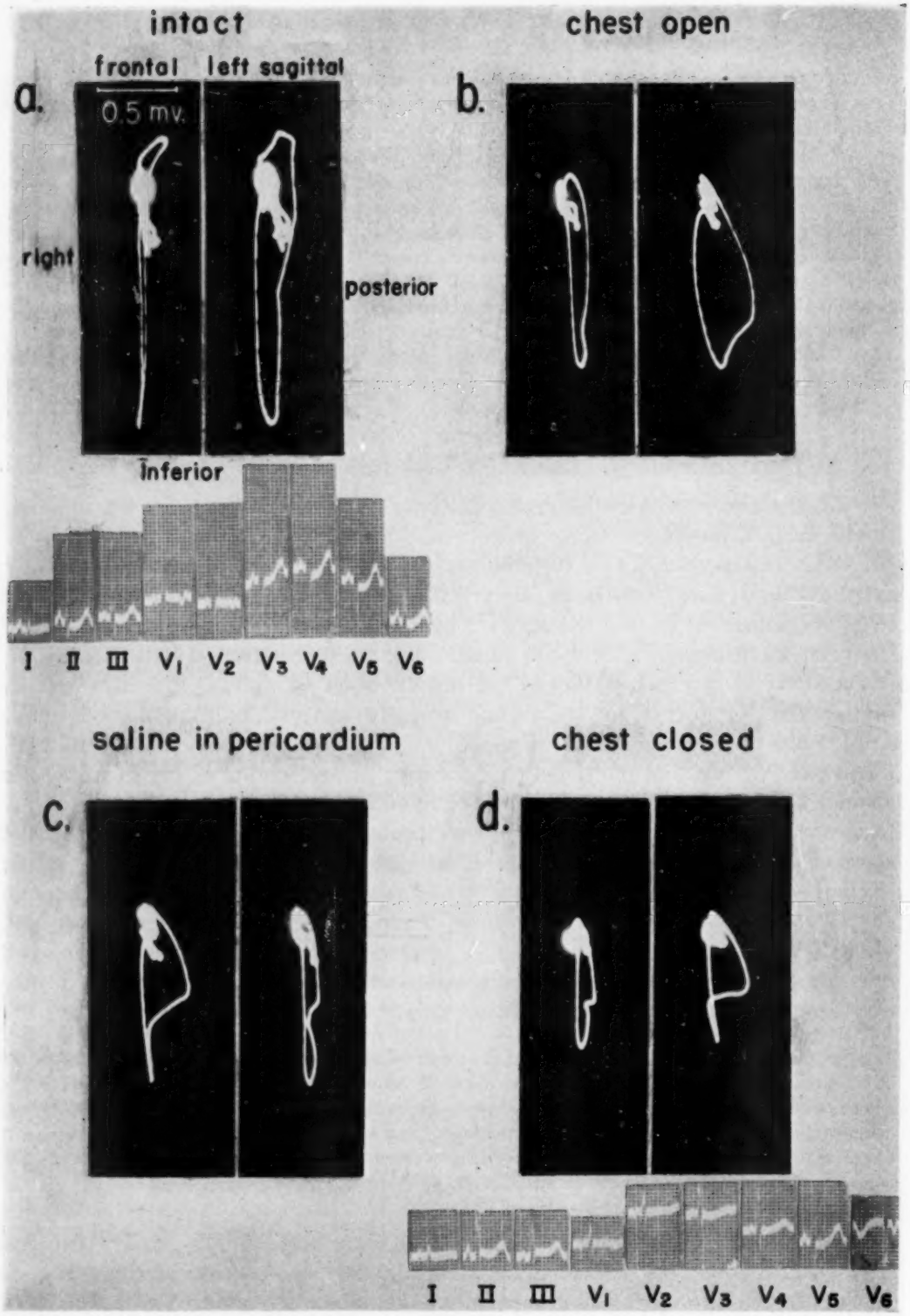


Fig. 1.—The sVCG showing change in configuration of the QRSsÊ loop that occurs when the chest of a dog (No. 509) is opened. The following tracings were recorded: (*a*) a supine, anesthetized dog before the procedure; (*b*) after the chest was opened; (*c*) after the pericardial sac was flushed with warm saline (37° C.); and (*d*) after the chest was closed. In this and subsequent illustrations, the scale for all views of each dog is that shown in one of the tracings, unless otherwise indicated. The plane projections of the sVCG illustrated are the frontal and left sagittal (i.e., the sagittal to the frontal as viewed from the subject's left).

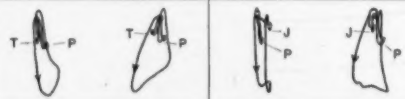
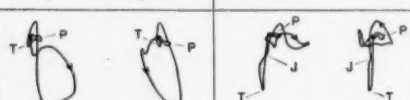
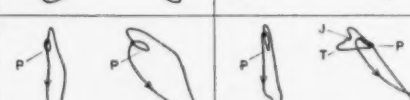
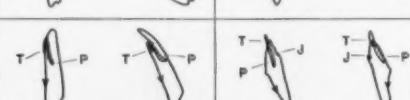
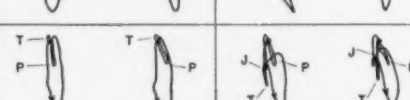
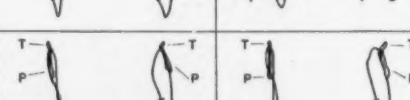
Dog No.	Site of burn	Size		VCG						Changes — Initial change ---- Return		
		Depth (mm.)	Diameter (mm.)	Before		After		Later				
				Frontal	Sagittal	Frontal	Sagittal	Frontal	Sagittal	Component	Frontal	Sagittal
501	Posterior wall near apex	4	30							Mid QRS J T		
502	Central lateral wall	3-4	40-50							Mid QRS Mid-late QRS Late QRS J T		
504	Posterolateral	3	25							Mid QRS Late QRS J T		
507	Central posterior wall (RVH)	4	20							Mid QRS J T (transient) P		
512	Anterior wall near apex	2	30							Afferent QRS J T		
513	Anterolateral wall	8	30-40							Early QRS Mid QRS Late QRS J T		
516	Posterior wall near apex	5-6	10-20							Early-mid QRS Mid QRS Late QRS J T		
524	Lateral wall									Early QRS		

Fig. 2.—A tabulation of changes in the sVCG of canine hearts which sustained burning of the left ventricular myocardium. These views are drawn from the original records. Solid arrows indicate the magnitude and direction of immediate changes, and dotted arrows indicate the magnitude and direction of "recovery" from these alterations.

sVCG and TsÊ loops were not recorded in sufficient detail in many of the traces but, in those in which satisfactory analysis was possible, spatial displacement of the S-T segmental portions and change in the TsÊ loops were always present and definite (Dog No. 513).

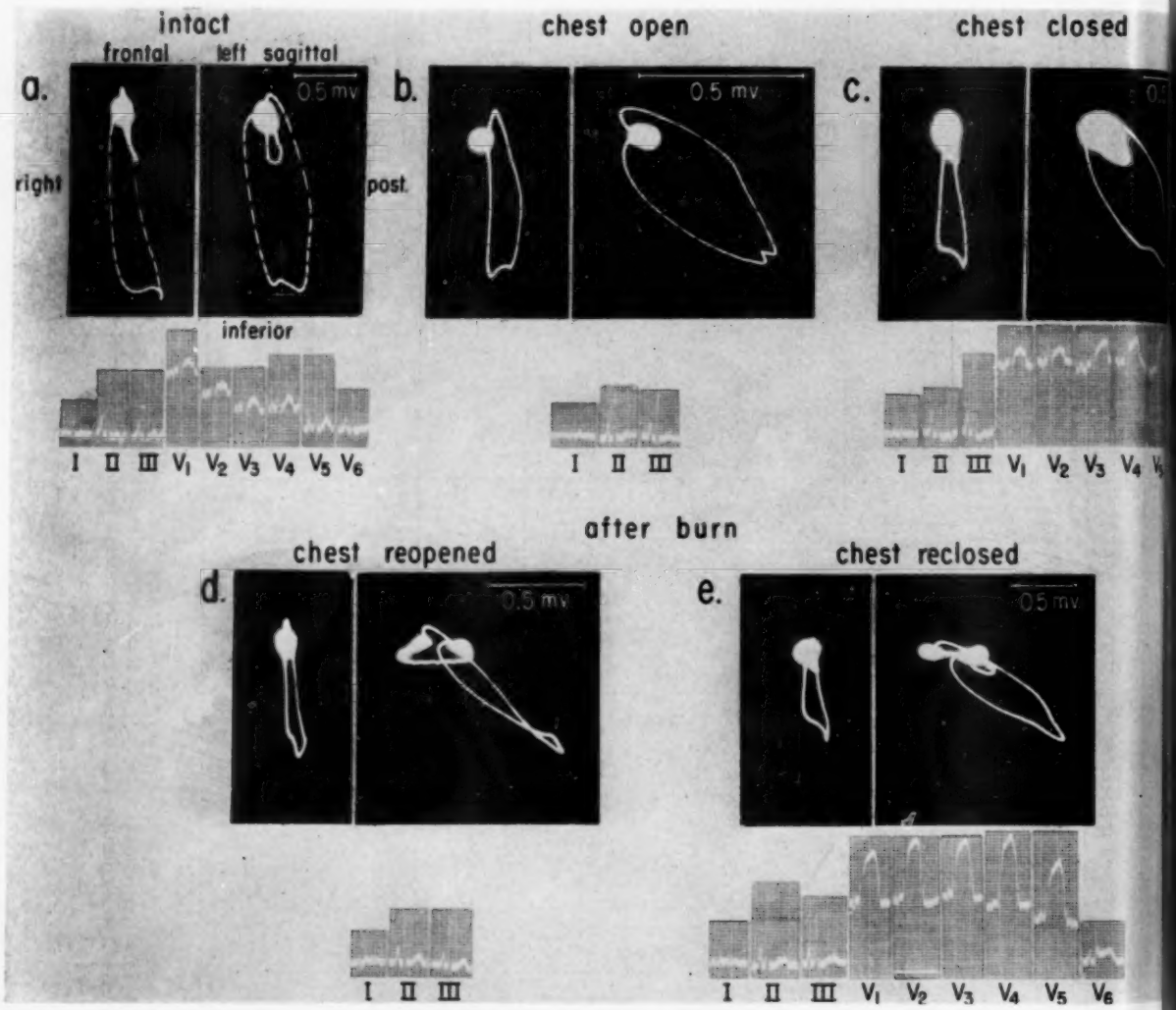


Fig. 3.—The sVCG in a burn of the anterior surface of the left ventricle of a dog (No. 512). The following views are shown: (*a*) initially, (*b*) after the chest was opened, (*c*) after the chest was closed, (*d*) after the chest was reopened and a burn 30 mm. in diameter and 2 mm. deep (at least) was inflicted on the anterior free wall near the apex, and (*e*) after reclosure. Note (*b*) the backward movement of the apex of the QRSsÊ loop in the sagittal view produced by opening of the chest, (*c*) the slight decrease in amplitude and change in configuration produced by closure, (*d*) the diminution in magnitude of displacement of junction, J, with the passage of time after burning, and (*e*) then after reclosure of the chest.

Burns of the Anterior Surface of the Left Ventricle.—The anterior surface of the left ventricle was burned in five of the twelve dogs. Fig. 3 shows an sVCG in which the changes were most striking; the associated changes in the ECG are also illustrated. The most consistent change in the QRSsÊ loop was the reduction in magnitude of its component vectors, especially those occurring during essentially the midtemporal portion. The early portions of the QRSsÊ loop, as

well as its general spatial orientation, were altered slightly, if at all (Fig. 3). The changes associated with the burns were influenced slightly, but definitely, by exposure of the heart to the atmosphere when the chest was opened (Dog No. 512).

The number of satisfactory TsÊ loops recorded was too small to permit any generalization regarding changes in this component of the sVCG. The TsÊ loop was consistently altered in configuration and magnitude, but only slightly in spatial orientation (Fig. 3). Associated with

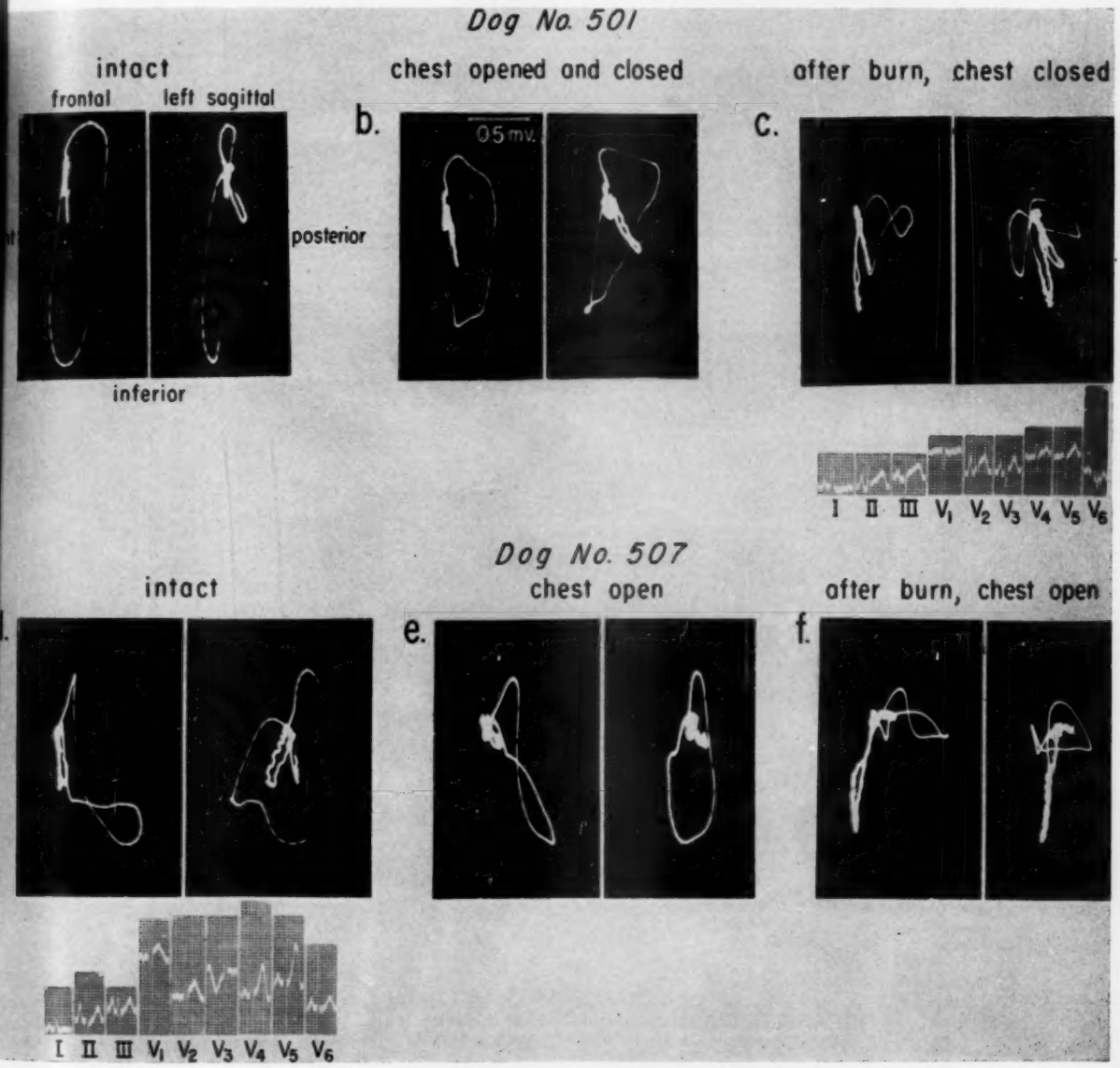


Fig. 4.—The sVCG of burns of the posterior surface of the left ventricle of Dog No. 501. In the upper series, records are shown of (*a*) the initial appearance of the sVCG, (*b*) after the chest was opened and closed, and (*c*) after the chest was reopened and a burn 30 mm. in diameter and 4 mm. deep was produced on the posterior wall near the apex, and then the chest was reclosed. The lower set of views illustrates (*d*) an initial sVCG of Dog No. 507, (*e*) the change in sVCG after the chest was opened, and (*f*) the sVCG with the chest still open but following production of a burn 20 mm. in diameter and 4 mm. deep on the posterior wall midway between base and apex. Note in *e* and *f* the pronounced shortening and elevation of the midportion of the QRSsÊ loop without early "Q" change. Extreme downward displacements of J and TsÊ loop are also present.

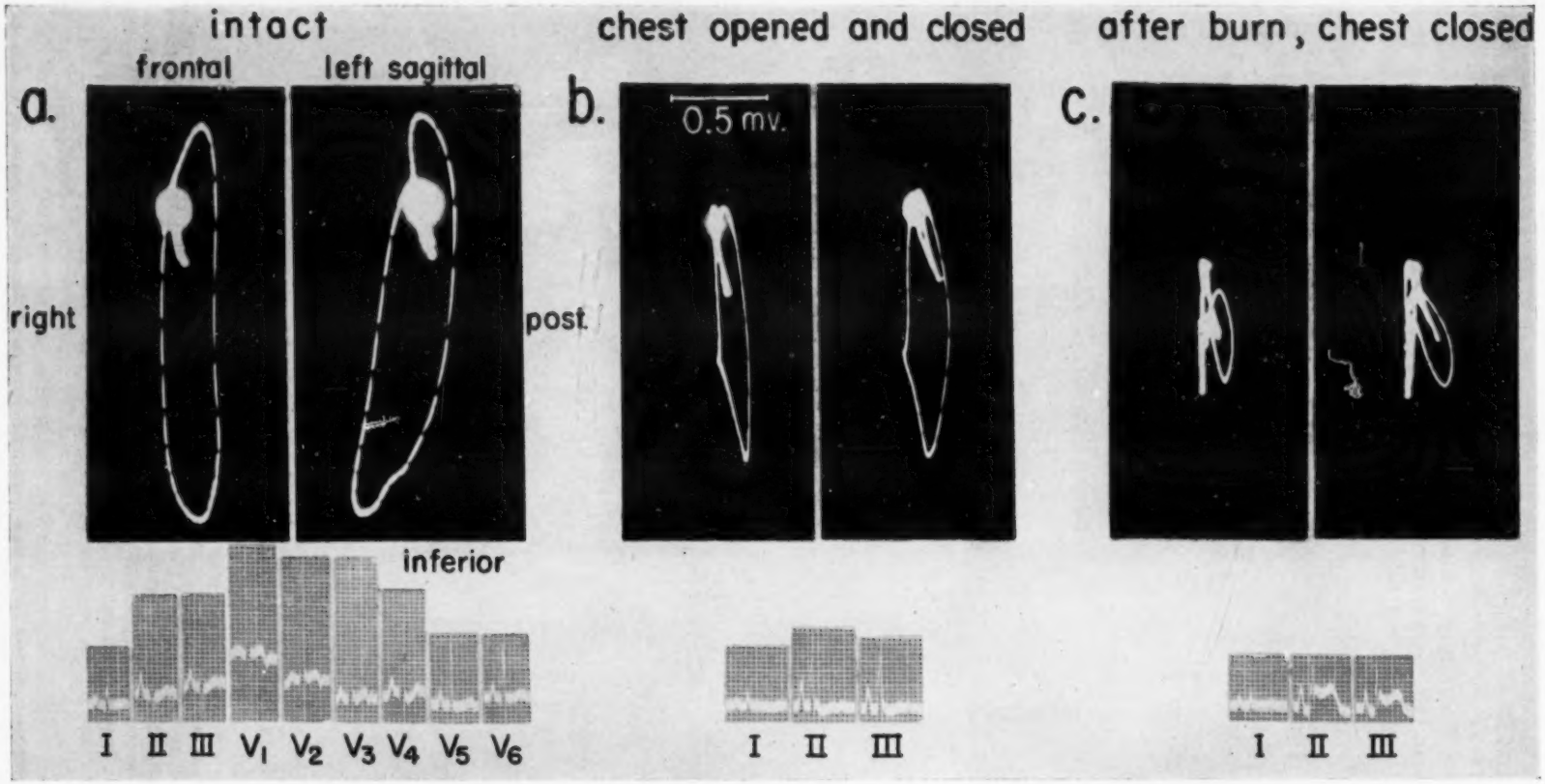


Fig. 5.—The sVCG after burn of the posterior surface of the left ventricle of a dog (No. 516). These views show (*a*) the initial appearance, (*b*) effect of opening and then closing the chest, and (*c*) alterations after production of a burn 6 mm. deep and 20 mm. in diameter on the posterior wall near the apex. Similar changes to those seen in Fig. 4 are present in *c* but are dwarfed by the extreme reduction in size. Note the notch in R_2 and R_3 of the accompanying electrocardiogram.

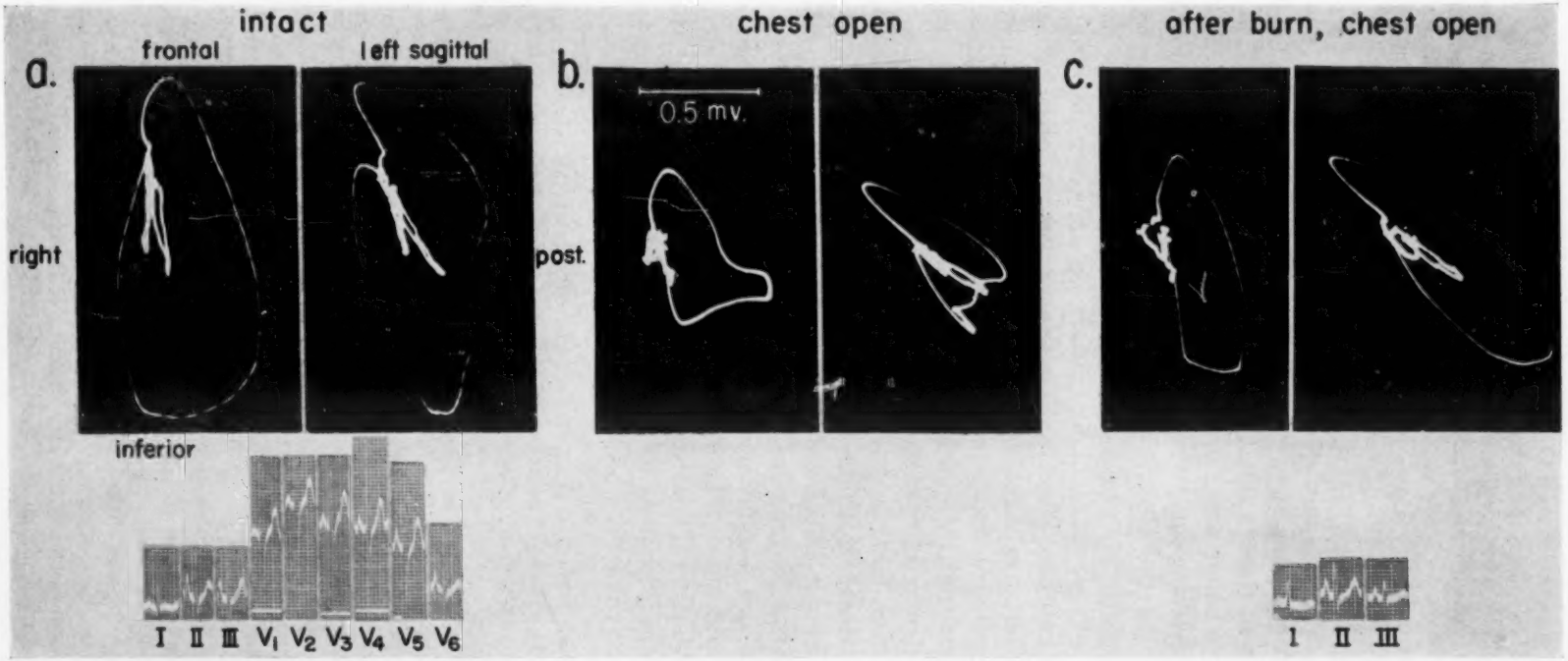


Fig. 6.—Distortion in the QRSsÊ loop developing prior to burning of the region of the pulmonary conus of a dog (No. 508). These views include (*a*) the initial sVCG, (*b*) deformity of the QRSsÊ loop after the chest was opened, which persisted until (*c*) a superficial burn of the pulmonary conus region was inflicted, after which the configuration changed again.

displacement of the S-T segment of the ECG was displacement of the corresponding component of the sVCG (Dog No. 512) toward the direction of the cardiac area that was burned. The TsÊ loop, on the other hand, tended to be displaced spatially away from the burned area or to be displaced further if that spatial orientation and displacement existed prior to burning of a particular area of the myocardium. These displacements were usually slight and required, in most instances, comparison with the sVCG recorded prior to injury for definite determination of the direction of displacement.

Comment.—Burning of a fairly large area of the anterior surface of the left ventricle to a depth equal to more than half the thickness of the wall always produced changes, even though small, in configuration of the QRSsÊ loop of the sVCG. The primary change was a decrease in magnitude of the mean instantaneous vectors inscribed during approximately the midtemporal portion of the loop, indicating alteration in the electric potentials produced relatively late rather than early during the process of depolarization. The associated ECG revealed notching, slurring, and decrease in magnitude of the corresponding temporal portions of the QRS complex (Fig. 3). These experimental observations tend to confirm impressions obtained from a study of the sVCG in human infarction.[1,2]

Changes in magnitude and orientation of the various components of the sVCG and ECG produced by burning conformed well to existing concepts in electrocardiography,[3] except that more pronounced alterations were expected with destruction of such large areas as the outer half of the thickness of the left ventricular wall.[4,5] However, these experiments were acute (two to three hours in duration), and changes associated with inflammation and other reactions to injury, which require a longer time to develop, may be necessary to produce the pronounced changes encountered clinically in the QRSsÊ loop and QRS complex of the ECG of man. The observations reported herein, which conform with these well-known clinical observations, open avenues of study of the mechanism for these changes. Follow-up experiments extending over an interval of several days were not conducted in this study.

Burns of the Posterior Surface of the Left Ventricle.—Burns of the posterior surface of the left ventricle in four dogs produced changes essentially analogous to those for burns of the anterior surface, the directions of displacement of appropriate spatial vectors corresponding to the location of the burned area. All components of the sVCG changed, and two of the most pronounced alterations in the sVCG produced by burning of the left ventricle occurred in this group (Fig. 4). However, as with burning of the anterior surface of the left ventricle, the early portion of the QRSsÊ loop and initial portions of the QRS complex of the ECG were altered slightly, if at all. A Q_3 pattern developed in only one instance (Dog No. 507), for example. Again, the midtemporal portions of the QRSsÊ loop were altered most significantly (Dog Nos. 501 and 507). Changes in these mean instantaneous vectors were associated with slurring, notching, and reduction in magnitude of the corresponding sections of the QRS complex of the ECG. In general, the magnitudes of the corresponding mean instantaneous vectors of the QRSsÊ loop were reduced by one half or more (Fig. 5).

Burns of the Pulmonary Conus.—Superficial burns extending more than half way through the wall were produced over the region of the pulmonary conus and adjacent portion of the right ventricle in three dogs. When the chest was opened and the heart was exposed to the atmosphere, the sVCG (Fig. 6) of one dog was altered a great deal, primarily in configuration and magnitude of the P and TsÊ loops and in reduction in magnitude of those vectors of the QRSsÊ loop that are usually directed downward and to the left. Burning of the conus caused displacement of the junction and alteration in magnitude and spatial orientation of the TsÊ loop. Although the

TABLE I. THE sVCG IN LIGATION OF THE ACUTE CORONARY ARTERY

DOG NO.	SITE OF LIGATION	AREA OF CYANOSIS	sVCG CHANGES*			ECG CHANGES
			QRS	S-T OR J	T	
511 (Fig. 8, *d*, *e*, *f*)	Distal (septal) branch of anterior descending branch of left coronary artery	Anterior aspect of apex and over septum (also fibrin deposit)	(1) Early—upward, anterior, and to left (2) Middle—"arc deformity" with concavity toward apex	Forward	Downward	(1) Development of small Q_3 and slurred R_3; loss of Q in I and V_6 (2) Elevated S-T in anterior chest leads (3) Peaked T_3 and T in anterior chest leads
517 (Fig. 7, *a*, *b*, *c*)	Anterior descending branch of left coronary artery	Anterior aspect of apex	Little characteristic change			(1) Lowered voltage of QRS in anterior chest leads (2) Inversion of T in anterior chest leads
518 (Fig. 7, *d*, *e*, *f*)	Anterior descending branch of left coronary artery	Anterior aspect of apex	(1) Early—slow, posterior			(1) Lowered T in anterior chest leads
519 (Fig. 8, *a*, *b*, *c*)	Anterior descending, circumflex, and posterior descending branches of left coronary artery	All of anterior and posterior free walls except lateral border and basal aspect above ligatures	(1) Early—upward, anterior, and to right, prolonged or slowed (2) Middle—to right and posterior	Downward and posterior	With S-T	(1) Development of wide Q_2 and Q_3 (2) Elevated S-$T_{2,3}$ and depressed S-T in anterior chest leads (3) Heightened $T_{2,3}$ and T in anterior chest leads
520	Anterior descending, circumflex, and posterior descending branches of left coronary artery	Posterior free wall; (and pink-and-blue mottling of anterior free wall) except basal aspect above ligatures	(1) Early—upward, to right, and anterior (2) Middle—shortened (3) Late—slightly to right and anterior	Downward, posterior, and slightly to right	Up	Incomplete because of ventricular fibrillation, but Lead II shows development of wide Q_2 with elevation at S-T and T

*The directions noted here are those analogous to man in the anatomic position; for example, up is headward, forward is ventral, down is caudal, posterior is dorsal, etc.

QRSsÊ loop tended to revert to the original configuration, return was not complete. The vectorcardiograms of the other two dogs showed, mainly, effects of the operation and exposure of the heart to the atmosphere except for the transient appearance of an open TsÊ loop and displacement of the S-T segment immediately after the burn.

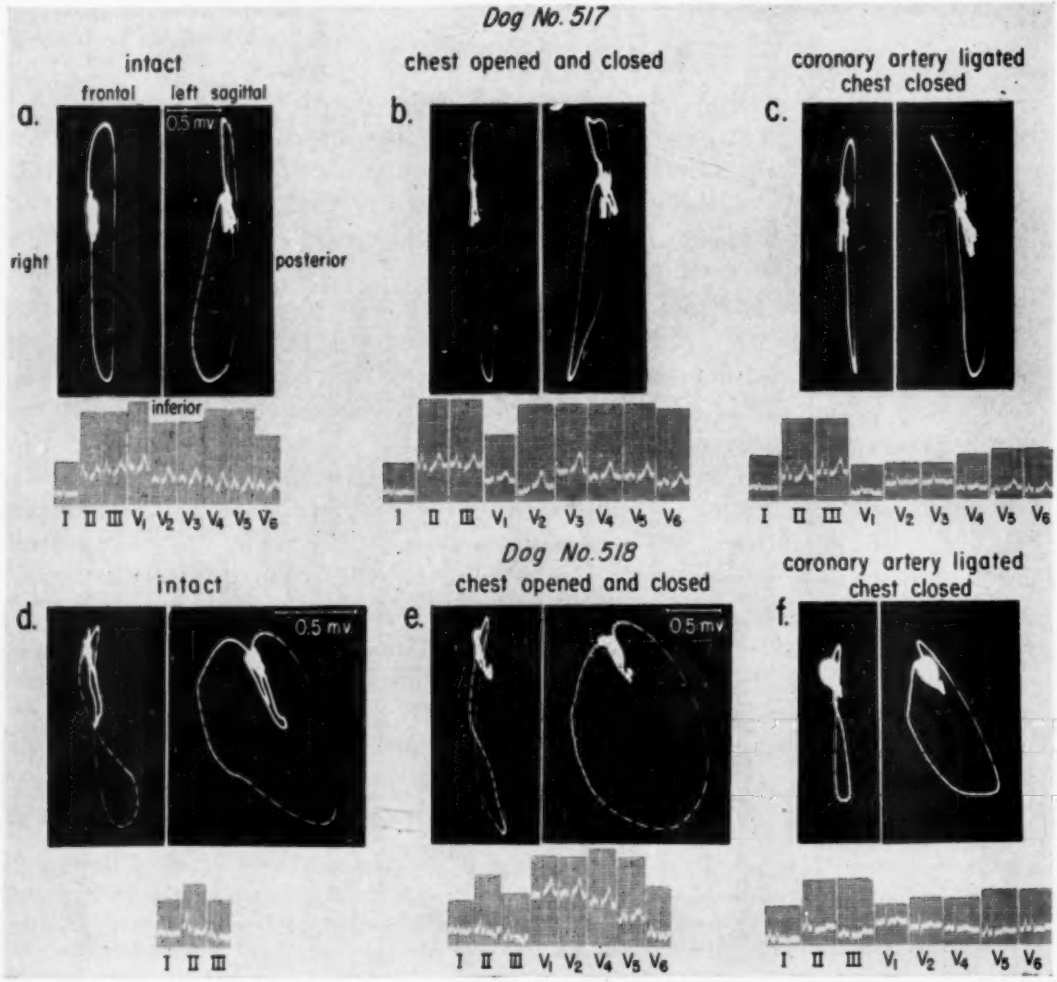


Fig. 7.—The sVCG after ligation of the left coronary artery of the dog, in which minimal deformity of QRSsÊ loop resulted. Shown are (*a* and *d*) initial sVCG's, (*b* and *e*) the tracings after opening and closing of the chest, and (*c* and *f*) final tracings after ligation of the anterior descending branch of the left coronary artery in each instance.

Comment.—Burning of the conus area tended to alter the sVCG less than did burning of portions of the left ventricle. The most interesting change observed in two of the three dogs in which the conus area was burned consisted of development of a horseshoe-shaped TsÊ loop without an associated readily discernible change in the T wave and S-T segment of the ECG (Fig. 6). Although the S-T segment and T wave were altered in conformity with the VCG changes, experience with these two types of recordings in the ECG would not have afforded ready prediction of such a TsÊ loop. In fact, the TsÊ loop was similar in many respects

to that described previously for left ventricular hypertrophy in man. The horseshoe-shaped TsÊ loop occurred in only one other dog in this series, in which the anterior surface of the left ventricle near the base of the heart and near the conus area was burned (Dog No. 512). The significance of this type of T change under these circumstances remains unknown.

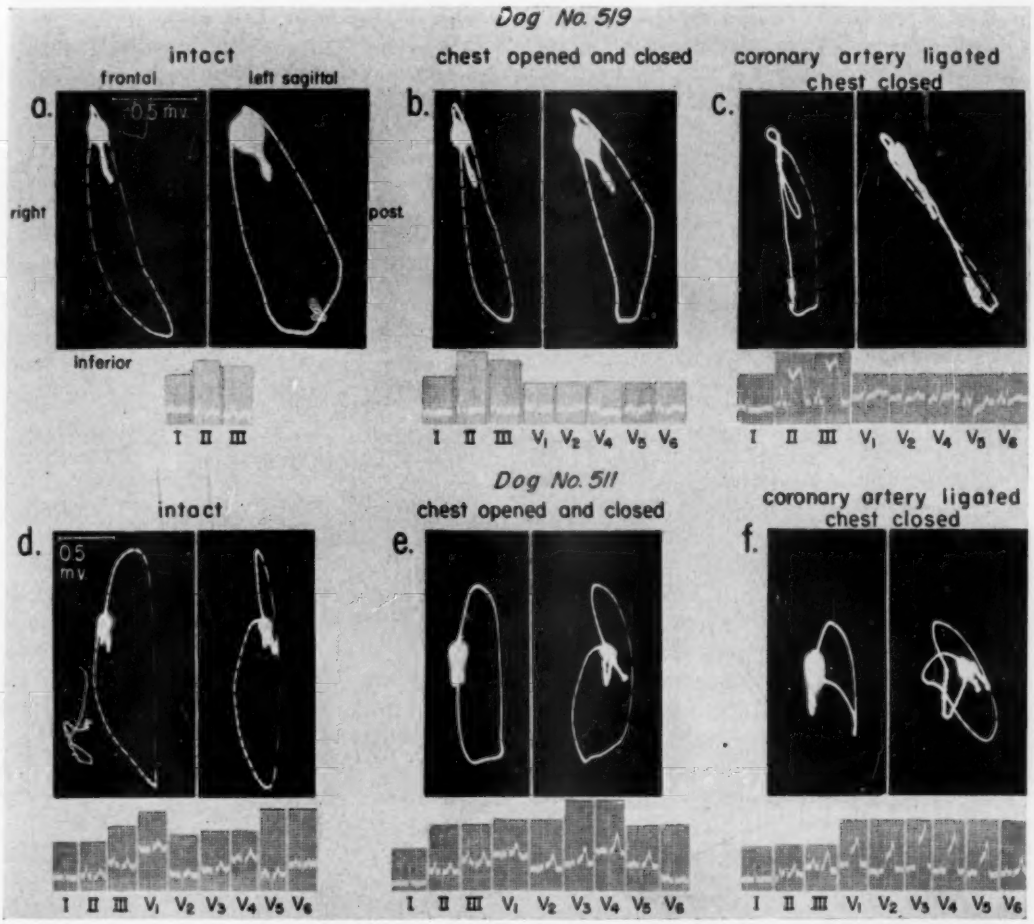


Fig. 8.—The sVCG in ligation of branches of the left coronary artery of the dog with classical changes of the QRSsÊ loop. Shown are (*a* and *c*) initial sVCG's and (*b* and *d*) control records with the chest opened and closed. *c*, Seventy-five minutes after ligation of the anterior descending, circumflex, and posterior descending branches of the left coronary artery in one animal, there is displacement of J downward and prolongation of the initial limb of the QRSsÊ loop upward and to the right with shift of the mid-limb posteriorly and to the left. The posterior wall showed a yellow pallor on gross section. *e*, In the other animal, two hours after ligation of the distal (septal) branch of the anterior descending artery, the QRSsÊ loop was extremely shortened and an early mid-limb "arc deformity" was present, suggesting that seen in apical myocardial infarction in man. Note that the only conventional QRS change in the ECG is the loss of R in Leads I and V_6. J is displaced anteriorly.

Ligations of Branches of the Left Coronary Artery.—Because unexpectedly little change developed in the sVCG and ECG following fairly extensive burning of the heart muscle, it was considered appropriate to observe the influence of ligation of a major coronary artery. One of the major branches of the left coronary artery was ligated in five dogs; the changes observed are summarized in Table I. Gross demarcation of the lesions was not sharp, but after two hours

the areas of electrically dead muscle were assumed to correspond to the "blue" areas of myocardium, although the "pink" and "mottled" areas may or may not have been intact electrically.

The changes produced in the sVCG and ECG of the five dogs did not appreciably differ from those described for the experiments in which the cardiac muscle was more discretely destroyed by burning. In two dogs (Fig. 7) the changes produced in the QRSsÊ loop and TsÊ loop were remarkably small; this, of course, was also true for the corresponding complexes of the ECG. On the other hand, in the three other dogs (Fig. 8), these changes were extensive, especially in the process of repolarization. In these three dogs the spatial displacement of the initial portion of the QRSsÊ loop, J, S-T components, and TsÊ loops was in accord with classical concepts in electrocardiography.[3] In Dog No. 511, the mean instantaneous vectors of the midtemporal portion of the QRSsÊ loop were decreased in magnitude, resulting in deformities similar to those previously described for myocardial infarction in man.[1,2]

Comment.—It is rather interesting that, in three of five dogs, ligation of the anterior coronary artery of the heart resulted in the classical change in the initial portion of the QRS complex and the corresponding portions of the sVCG but that this failed to occur in all the dogs in which the myocardium was burned. When the classical change occurred following myocardial infarctions produced by ligation of the coronary artery, the sVCG and corresponding ECG changes were similar to those already described for infarction in man[1,2] and conform to accepted principles in theoretic electrocardiography.[3,6,7]

Instillation of Formaldehyde in the Pericardial Sac.—Because of the nature of the results obtained with localized injury to the myocardium, uniform destruction of the subepicardial musculature over the entire surface of the heart was produced in seven dogs by injection of 50 c.c. or less of 40 per cent solution of formaldehyde into the pericardial sac. The results of a typical experiment are illustrated in Fig. 9, which shows serial changes in the sVCG and in Lead II of the ECG from the moment of instillation of the formaldehyde to death of the animal 10.5 minutes later. In each experiment, the progression of changes in the sVCG and ECG was almost identical. Changes in the sVCG were characterized by (1) development of a long, upwardly oriented TsÊ loop and (2) pronounced decrease in magnitude of the mean instantaneous vectors of the QRSsÊ loop with a characteristic "truncation" and elevation of the terminal portion of this loop. Thus, the dwarfing QRSsÊ loop was spatially oriented anteriorly, inferiorly, and to the left, but terminally developed into the uncoiled QRSsÊ loop corresponding to the component of depolarization of the almost monophasic curve found in Lead II.

The manifest component vectors of the QRSsÊ loop were finally considerably reduced (a maximum of essentially 33 per cent) in magnitude, and the configuration of the loop was greatly distorted from the initial pattern. The general spatial orientation of this loop was altered relatively little despite the corresponding monophasic type of configuration of the standard leads of the ECG (Fig. 9).

The greatest change in spatial orientation occurred in the TsÊ loop (Fig. 9). This loop increased in magnitude, was spatially oriented in a direction essentially opposite to the QRSsÊ loop, and tended to resemble those encountered in the experiments in which there was no monophasic configuration to the corresponding ECG. In fact, a study of Fig. 9 shows that, as the "ischemic" T-wave pattern of the ECG and sVCG at 52 seconds changed to the monophasic pattern ECG and sVCG at 630 seconds, the late TsÊ loop changed relatively little in configuration and spatial orientation.

In three dogs (Nos. 522, 525, and 528) in which a monophasic type of curve developed most fully in Lead II of the ECG, there was only an upstroke for the QRS complex of the ECG and only an efferent limb of the QRSsÊ loop of the VCG (Fig. 9). The remainder of the sVCG was TsÊ loop or was produced by the process of repolarization. Junction, J, under such circumstances was extremely displaced and located at the end of the efferent limb of the QRSsÊ loop. The changes in the PsÊ loop were highly variable and *not* characteristic.

Comment.—These experiments with formaldehyde were remarkably reproducible, certainly more so than those involving burning of the myocardium or ligation of the coronary arteries. The progression of changes in the sVCG and ECG was uniform from experiment to experiment. This type of injury can serve as a useful tool for the study of the electrical phenomena, intrinsic and manifest, of the myocardium.

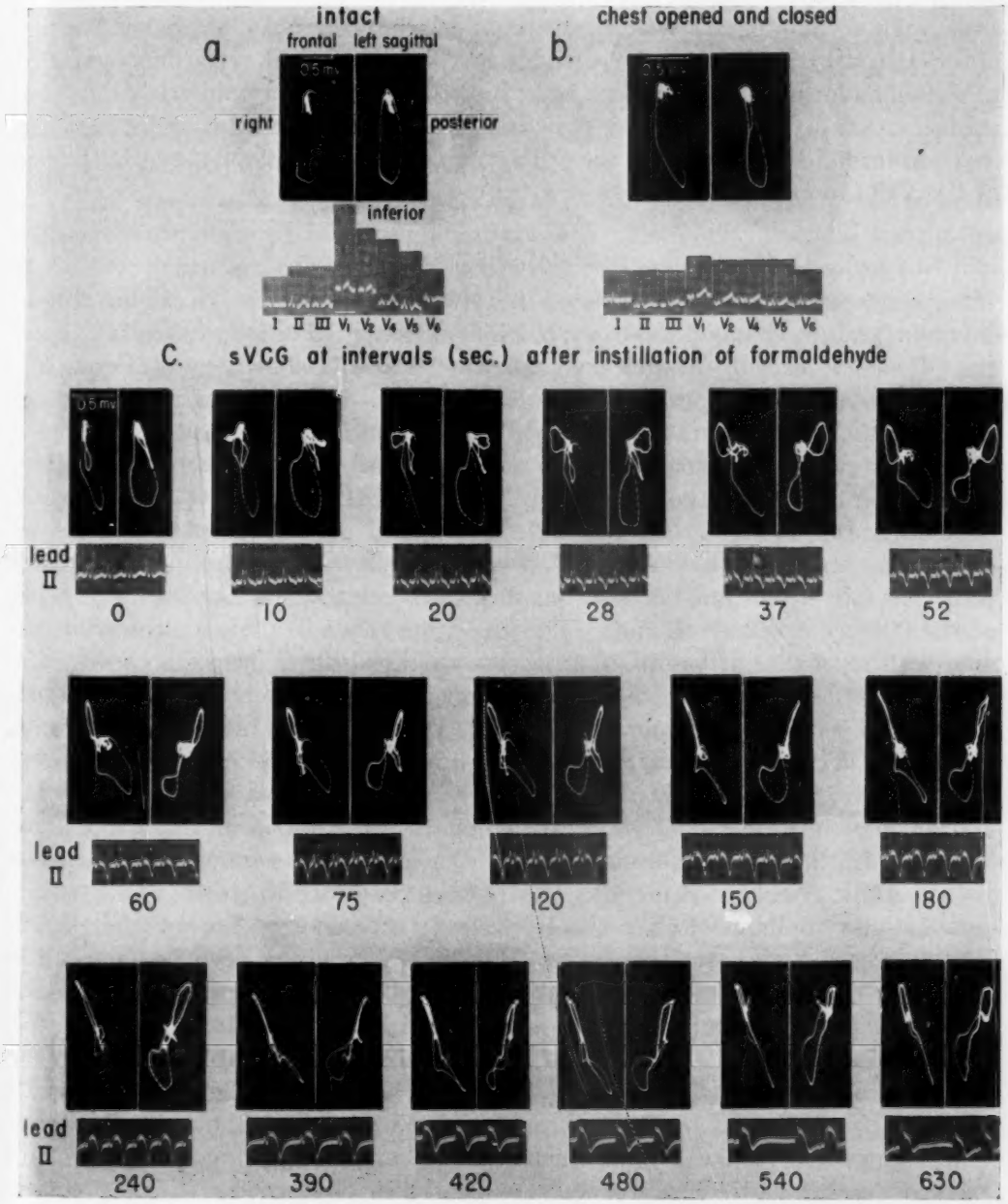


Fig. 9.—Progressive changes in the sVCG upon instillation of formaldehyde in the pericardial sac of Dog No. 527. *a*, The sVCG and ECG initially and *b*, after opening and closing of the chest. *c*, The series of sVCG's and accompanying fragments of Lead II are labelled according to the time after the beginning of an instillation of 50 c.c. of 40 per cent formaldehyde into the pericardial sac. The time required for instillation was forty-five seconds. See text for discussion of the sequence of alterations.

In these experiments, the outer third (up to 3 mm.) of the entire myocardium was demonstrably destroyed chemically, as observed at necropsy, but the depth of physiologic injury may have been more extensive, especially terminally. The septum did not appear to be damaged. Still, the QRS complex of the myocardium and QRSsÊ loop remained, being reduced in magnitude by no more than one-third.[4,5] This change in magnitude was not caused by the fluid in the pericardial sac, for its removal altered the records slightly, if at all. An experiment of this type with formaldehyde was kindly conducted by Dr. A. M. Scher,[8] whose observations with intramural electrodes revealed continued early depolarization of the subendocardial layers of the heart but silence in the formaldehyde-damaged subepicardial layers. Diffuse destruction of the outer one-third or more of the myocardium did not eliminate the QRS complex of the ECG or the QRSsÊ loop of the VCG in our experiments.

GENERAL DISCUSSION

An aspect of particular interest in these studies was that local burning of the myocardium changed the early portions of the QRSsÊ loop of the VCG and the QRS complexes of the ECG only slightly, if at all. The Q type of complex, so characteristic of myocardial infarction in man, did not develop in the dogs in which the myocardium was burned, regardless of the area burned, nor did it develop in two of four dogs in which a major branch of the left coronary artery was ligated. Most of the alterations in the QRSsÊ loop and QRS complexes developed approximately during the midtemporal portions of the processes of depolarization. Injury or destruction of portions of myocardium that are depolarized late would not be expected to produce changes in the initial portions of the QRS complex or sÊ loop. The late appearance in the time course of depolarization of alterations of this process would also not be expected to alter the conventional electrocardiogram. Furthermore, in the presence of lateral myocardial infarction, an abnormally wide Q wave in any one or a combination of Leads I, V_L, or V_6 does not necessarily imply that the extremely early electrical activity is abnormally produced. In such instances, normal septal depolarization may initiate the Q wave, to which the effects of infarction later contribute. With the possible exception of the experiments involving ligation of the coronary artery, such merging effects were not noted in these studies.

The development of classical alteration in the early portions of the QRSsÊ loop and QRS complex in three of five dogs in which a large coronary artery was ligated suggests that the electrical manifestations of the myocardial injury caused by obstruction to coronary arterial flow differ from those produced immediately by burning. Similarly, the classical ECG manifestations of infarction may not develop immediately with the initial injury. Ligation of the coronary artery probably immediately produces a more diffuse injury with more subendocardial damage and resultant impairment of depolarization of those portions of the myocardium that are usually activated early in the process. The effects of burning, however, make it evident that localized destruction of cardiac muscle can exist without alterations in the early portions of the QRSsÊ loop and QRS complexes, whereas the later portion of these complexes may be altered. More

detailed ECG recording may permit recognition in the total record and ready identification of these later changes with consequent better clinical interpretation.

One of the difficulties encountered in these experiments was concerned with correlation of the anatomic boundary with that of electrophysiologic abnormality. Although the sites of gross damage were evident on histologic examination, some areas may have been altered electrophysiologically without obvious anatomic changes. The electrocardiographically "silent" areas of the heart were perhaps fairly large in some instances of acute injury, an important problem in electrocardiography. Nevertheless, the changes produced in the sVCG and the ECG by burning of the myocardium and by ligation of the coronary artery were more or less predictable,[5-7] although more extensive changes were expected at the outset of these experiments.

The mechanism for the changes in the sVCG and ECG following instillation of formaldehyde in the pericardial sac is not clear. It would appear that a greater percentage of the right than of the left ventricle was destroyed. This would tend to cause the electrical activity to be more of left than of right ventricular origin, with resultant spatial orientation of the respective components of the sVCG. Destruction of left ventricular muscle mass must have been responsible in large part for the reduction in magnitude of the mean instantaneous vector quantities of the QRSsÊ loop. Although the degree and nature of alterations in coronary circulation remain unknown, the extreme shifting of the S-T segment of the ECG and corresponding component of the sVCG, as well as the alterations in the TsÊ loop, must be due, in large part, to the shell of injury and destruction that extended over the entire surface of the ventricles. Because of the premortal changes in configuration of the QRSsÊ loop associated with the prominent S-T shift, a final estimate of the reduction in magnitude of the QRSsÊ loop is difficult. The monophasic type of curve that developed could be explained by such longstanding concepts in electrocardiography as the idea that the QRS and T complexes of the ECG are composed of two monophasic action currents, one of subendocardial origin and the other of subepicardial myocardial origin. In this instance the contribution of the subepicardial component would be minimal, perhaps leaving a relatively intact left ventricular subendocardial "polarized membrane," the gradual depolarization of which might result in the "upright" QRS in all standard leads and an open, linear QRSsÊ loop. Such explanations, tentatively derived, can be only conjectural. The mechanism for the highly variable and unpredictable changes in the PsÊ loop following instillation of formaldehyde in the pericardial sac also remains unknown.

SUMMARY

Superficial myocardial destruction was performed, in acute experiments, on 27 dogs by burning with soldering iron, torch, or electrocautery and by pericardial instillation of formaldehyde.

The effect on the QRSsÊ loop of superficial localized myocardial loss was either not detectable or, more often, led to the appearance of a small deformity in the direction predicted by present-day electrocardiographic concepts. Similarly, shifts in S-T vectors and orientation of TsÊ loops, when recorded, were in the predicted direction.

The use of a fixative, such as formaldehyde, is suggested as a possible means of producing acute and relatively discrete lesions in the study of the relations between the anatomic site and the electrical activity of cardiac muscle.

REFERENCES

1. Burch, G. E., Horan, L., Abildskov, J. A., and Cronvich, J. A.: Circulation **12**:418-425, 1955.
2. Burch, G. E., Horan, L., and Cronvich, J. A.: Circulation **13**:360-367, 1956.
3. Burch, G. E., and Winsor, T.: A Primer of Electrocardiography, ed. 3, Philadelphia, 1955, Lea & Febiger.
4. Prinzmetal, M., Shaw, C. McK., Maxwell, M. H., Flamm, E. J., Goldman, A., Kimura, N., Rakita, L., Borduas, J. L., Rothmann, S., and Kennamer, R.: Am. J. Med. **16**:469-489, 1954.
5. Maxwell, M., Kennamer, R., and Prinzmetal, M.: Am. J. Med. **17**:614-628, 1954.
6. Ashman, R., and Hull, E.: Essentials of Electrocardiography for the Student and Practitioner of Medicine, ed. 2, New York, 1941, The Macmillan Company.
7. Bayley, R. H., and LaDue, J. S.: AM. HEART J. **28**:54-68, 1944.
8. Scher, A. M.: Personal communication.

TECHNIQUE AND SEQUELAE OF CATHETERIZATION OF THE LEFT SIDE OF THE HEART

MARIANNE BAGGER, M.D., VIKING OLOV BJÖRK, M.D., AND GUNNAR MALMSTRÖM, M.D.

STOCKHOLM, SWEDEN

EARLY 1953 we introduced a technique of puncture of the left atrium with a needle through the eighth intercostal space in the right posterior portion of the thorax.[1] This technique permits the introduction of a fine plastic catheter through the needle down into the left ventricle and out into the aorta. Thus a complete left heart catheterization with the measurements of the pressure gradient across the mitral and aortic valves can be performed. The puncture technique has also permitted the rapid injection of contrast medium in the left atrium for outlining the mitral valves during the heart cycle, which has proved to be of a practical value. In cases difficult to evaluate, especially with combined lesions, we consider this method of left heart catheterization, if necessary in combination with angiocardiography, to be of great clinical help, so we have applied it in 167 cases and we will continue to do so in selected cases.

The aim of this paper is to report the original technique as well as the complications we have had.

TECHNIQUE

In order to make left heart catheterization a practical procedure, rapid and easy to carry out, we have omitted fluoroscopic control. Therefore it only takes fifteen to twenty minutes to perform and it is usually carried out after the completion of several hours' right heart catheterization with exercise tests.* Localization is facilitated by the application of indicators during a roentgen investigation one day earlier. In most patients the needle is introduced 6 to 7 cm. to the right of the midline above the ninth rib. In cases with an enlarged left atrium this technique has proved adequate without fluoroscopic control. For catheterization a light premedication and local anesthesia may be used, but for angiocardiography we use general anesthesia.

A 20 cm. long needle of 1.5 mm. outer diameter and 1.0 mm. inner diameter (Stille, Stockholm) is used. A skin wheal of ½ per cent procaine without adrenaline is made and more procaine is then injected through the needle as it is

From Sabbatsberg Hospital, Stockholm, Sweden.
Received for publication July 3, 1956.

*The patient is lying on his left side slightly rotated forward.

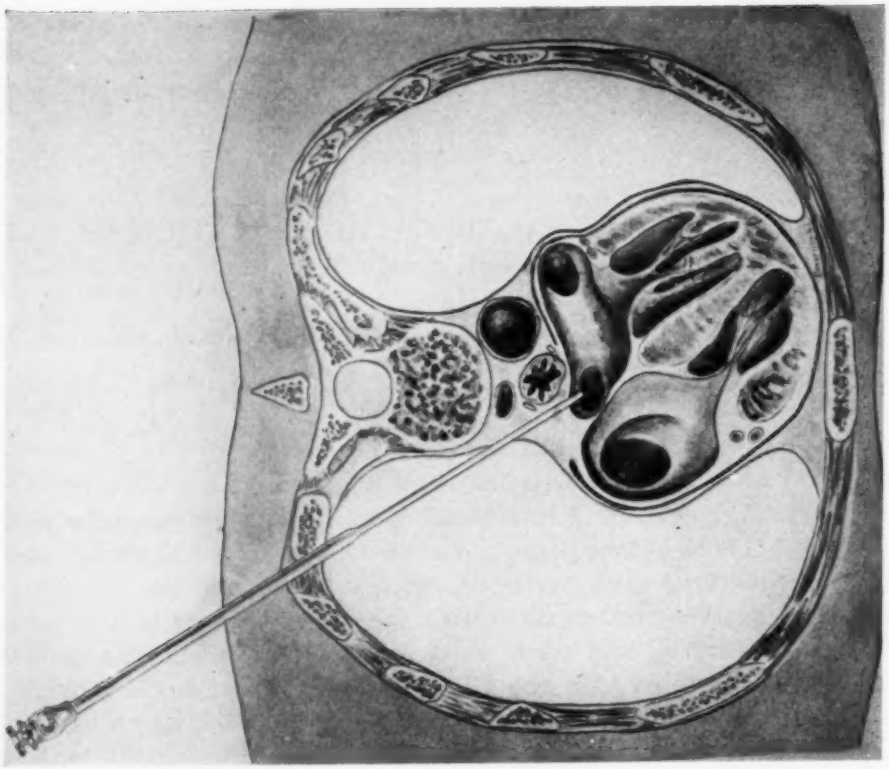


Fig. 2.

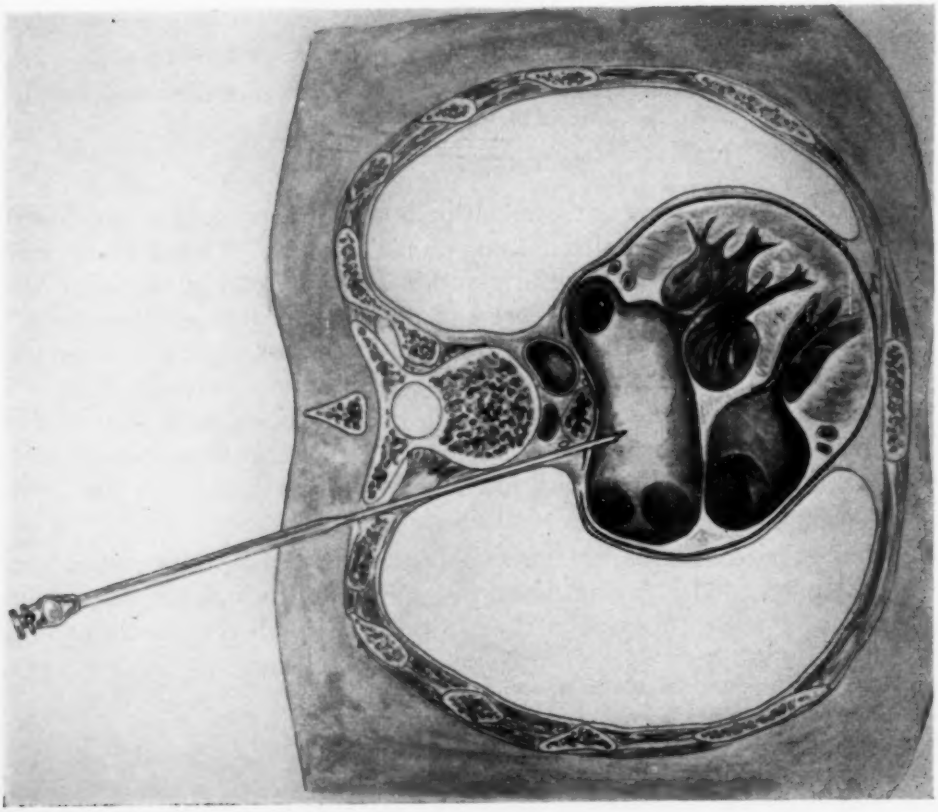


Fig. 1.

Fig. 1.—The needle is introduced paravertebrally from the right side into the left atrium.
Fig. 2.—When there is a small left atrium the needle is introduced through the lung from the right side.

introduced into the auricle. The needle is introduced until it hits the vertebral body when it is retracted a few millimeters and reintroduced lateral to the vertebral body (see Figs. 1, 2, and 3). The cardiac impulse can usually be felt via the needle before the tip is felt to pass through the wall of the left atrium, where bright red blood is aspirated and a left atrial type of pressure pulse is obtained. A blood sample from the left atrium is found to have an oxygen tension slightly higher than in the brachial artery. A thin plastic catheter is introduced through the needle down into the left ventricle and out into the aorta for pressure measure-

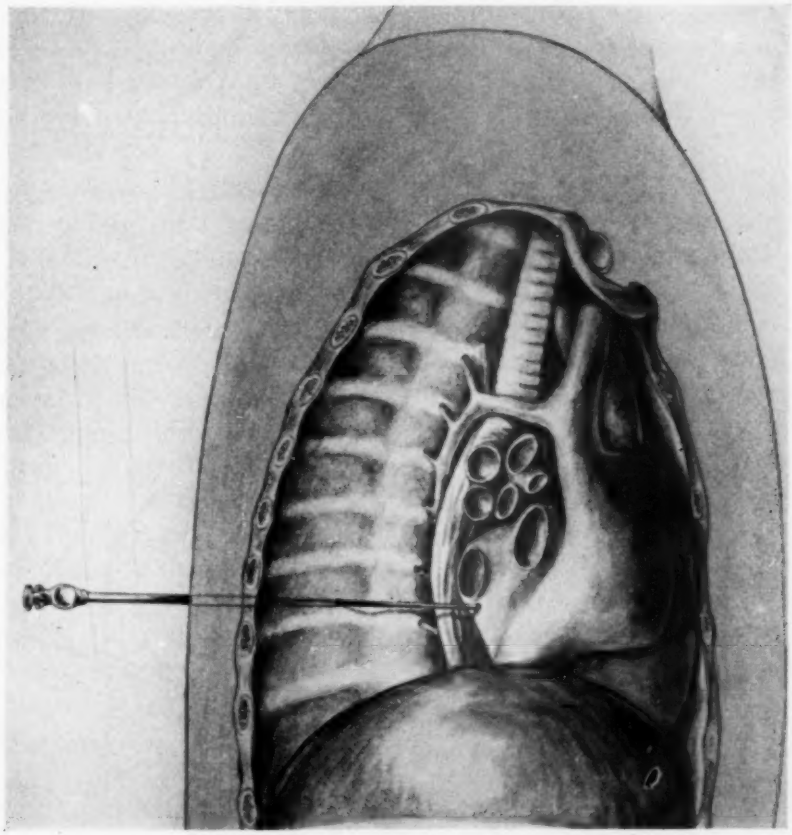


Fig. 3.—Lateral view of the needle in position in the left atrium.

ments (see Figs. 4 and 5). It is not always possible to get the catheter out into the aorta. Then a brachial artery pressure curve simultaneously obtained as the left ventricular pressure curve is of the same diagnostic value as the withdrawal curve across the aortic valves. It has always been possible to get the catheter down into the left ventricle. However, in some cases the catheter is, after a few heart beats, thrown back to the left atrium time after time and only short tracings from the left ventricle are obtained. This finding has been consistent with a dominating mitral insufficiency. When the catheter is in the left ventricle ventricular extrasystolies, sometimes in a series, are usually observed.

Fig. 4.

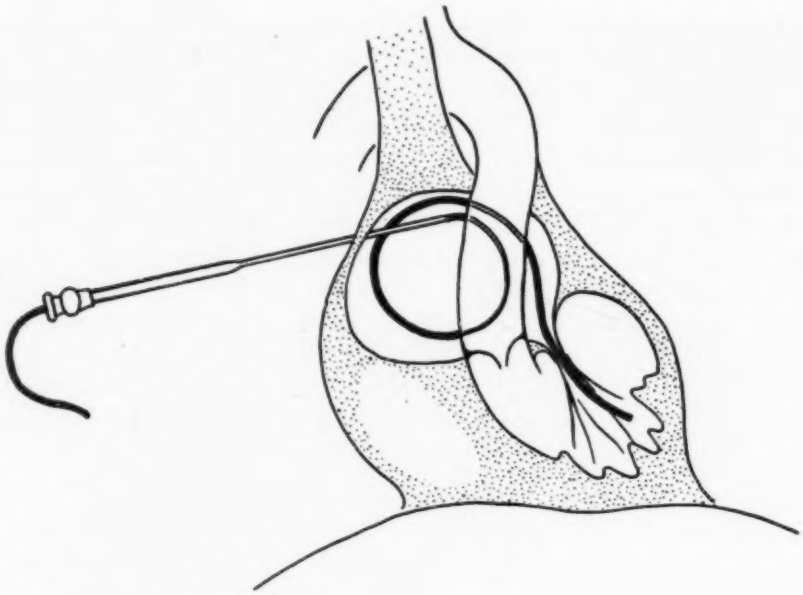
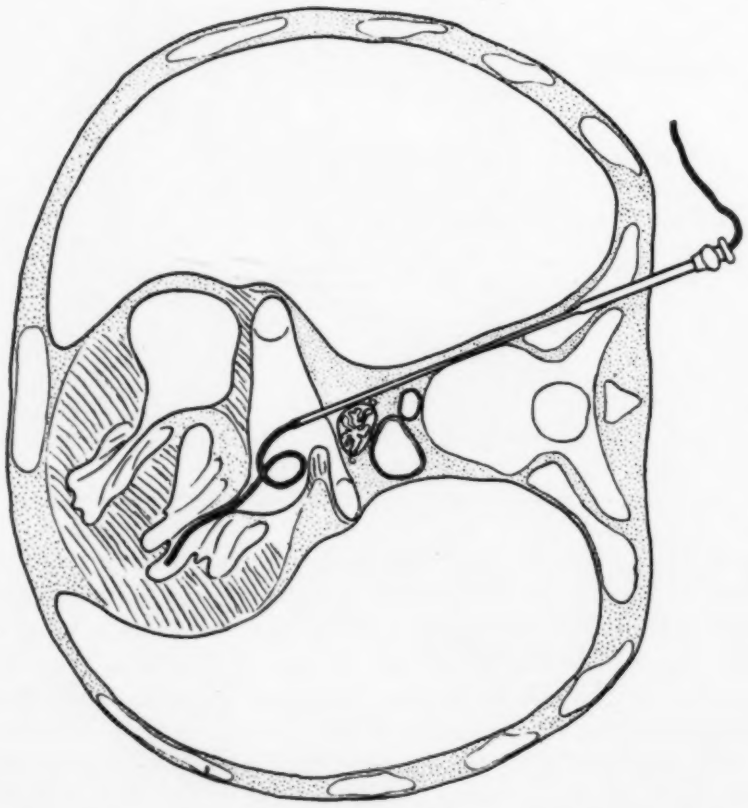


Fig. 5.



Figs. 4 and 5.—Diagrams showing the plastic catheter introduced through the needle down into the left ventricle.

SEQUELAE

Pain.—After a left heart catheterization the patients experience some pain in the right chest for a few hours up to a few days. This pain is felt when the patient is taking deep breaths and is probably due to a very small amount of blood in the right pleura.

Fever.—Many patients have a slight rise of temperature, i.e. 38° C., in the evening after the catheterization.

Hemopericardium.—There is always some leakage of blood into the pericardium. At the subsequent operation, therefore, usually a small amount of serosanguineous pericardial fluid is found and in some patients a small quantity of frankly bloody fluid. Only once has the blood in the pericardium caused fibrinous adhesions between the heart and the pericardium. These were, however, easy to separate.

The pleuritic pain, the extrasystolies, a slightly elevated temperature, and a small amount of blood in the pericardium are commonly encountered following a left heart catheterization. These sequelae are of short duration and not counted as complications.

As *major complications* are considered heart tamponade, ventricular fibrillation, and cerebral embolism. As *minor complications* are counted a small pneumothorax, hemoptysis, and a pleural effusion. Most of these minor complications would never have been detected if not every case had repeated chest roentgenograms after the left heart catheterization. Furthermore in evaluating the method it is necessary to consider the bad risk group of patients investigated. One patient with mitral stenosis and an aortic stenosis with a pressure gradient of 20 mm. Hg across the aortic valves had only a mitral commissurotomy performed. He did not improve after this operation and one year later he was readmitted to the hospital for another left heart catheterization with angiocardiography. While awaiting this investigation he suddenly died.

The danger of severe arrhythmia is probably greater in cases with badly oxygenated hearts due to aortic stenosis than in cases with mitral stenosis.

Left heart catheterization was performed in 128 cases and was without complications in 71 cases. Fifty-one cases had minor complications. Six cases (or 4.7 per cent) had major complications.

Angiocardiography through the needle in the left atrium was performed in thirty-nine cases.* Of these, twenty-two were without complications, nine with minor complications, and eight (or 20.5 per cent) had major complications.

The complications have therefore been more common in cases where angiocardiography has been added to the left heart catheterization. (The difference is highly probable [$0.01 > P > 0.001$]). This may be explained by the fact that the most difficult cases to evaluate have been selected for angiocardiography. Furthermore a general anesthesia has to be added to patients with a severe heart disease.

---

*The angiocardiography was performed at the x-ray department of The Pediatric Clinic, Caroline Hospital, under the direction of S. R. Kjellberg, M.D.

The oldest patient investigated with angiocardiography was a 64-year-old woman with constrictive pericarditis. Left heart catheterization showed a mean pressure of 20 mm. Hg in the left atrium. A selective angiocardiography was therefore performed in order to exclude mitral valvular disease. Before the angiogram was taken 12 liters of ascitic fluid was removed from the abdomen. The angiocardiography showed normal mitral valves and the patient withstood the procedure as well as a pericardiectomy.

MAJOR COMPLICATIONS

All together fourteen patients have had major complications, which will be reported in detail, as an early and well-planned treatment may prevent any ill effect of the complication (see Table I).

TABLE I. SEQUELAE OF LEFT HEART CATHETERIZATION IN 167 PATIENTS

MAJOR COMPLICATIONS	MITRAL LESIONS	AORTIC LESIONS
Cardiac tamponade with ventricular fibrillation	–	2
Transient ventricular fibrillation	1	–
Transient heart standstill	1	–
Transient hemiplegia	1	–
Hematothorax (350 ml.)	1	–
Pneumonia	1	1
Pneumonia and pericarditis	2	–
Catheter complications	2	–
Wrong contrast injection	2	–
Total	11	3

1. Cardiac Tamponade.—Two cases of aortic valvular lesions were complicated by cardiac tamponade. A 48-year-old woman with cavitary pulmonary tuberculosis had an aneurysmatic dilatation of the ascending aorta due to a syphilitic aortitis. The investigation of her heart was made for evaluation of the possibility of performing a segmental resection. The needle was introduced through the lung lateral to the bulging aneurysmatic aorta. The needle passed through the small and compressed left atrium into the aorta. From the hole in the syphilitic wall of the aorta there was considerable bleeding with cardiac tamponade. Too long a time passed until the patient was intubated and ventilated and ventricular fibrillation occurred. Thoracotomy was performed with evacuation of blood from the pericardium and restoration of normal heart rhythm by electric shock, but brain damage due to anoxia had occurred. After six hours there was still bleeding from the hole in the aorta and it was necessary to perform another thoracotomy and place a skin graft around the base of the aorta over the puncture hole. The patient died thirty-six hours later and never regained consciousness. The lethal outcome might have been prevented if instruments for intubation had been at hand immediately.

The second case of cardiac tamponade was aortic stenosis and angiocardiography was planned. As the pressures cannot be measured through the thin

plastic catheter in the x-ray department atypical mean pressure curves were obtained from the left ventricle. The needle was therefore withdrawn and inserted several times when cardiac tamponade occurred. Thoracotomy with evacuation of blood from the pericardium and defibrillation of the heart by electric shock as well as a transventricular valvulotomy of the stenosed aortic valves was performed on the roentgen table.*

2. *Ventricular Fibrillation.*—In one case electrocardiographic evidence of ventricular fibrillation was found immediately after the angiocardiography. The patient was inadequately ventilated after the anesthesia. Regular rhythm returned spontaneously after ventilation with 100 per cent oxygen.

3. *Heart Standstill.*—In one case a heart standstill of five seconds' duration immediately after the angiocardiography was detected on the electrocardiograph. Normal heart rhythm returned and the condition was not detected clinically.

4. *Embolism.*—One patient with a myxoma in the left atrium simulating a mitral stenosis had a transient hemiplegia. The needle had probably caused embolization from the tumor. A correct preoperative diagnosis could, however, be made. No late sequelae remained.

5. *Hematothorax.*—In one case it was necessary to aspirate 350 ml. of blood from the right chest.

6. *Pneumonia.*—Four cases were complicated with pneumonia, and in two of these there was, as well, a pericarditis. The leakage of contrast medium along the needle is thought to be responsible for one of these complications.

7. *Catheter Complications.*—The plastic catheter was cut by the tip of the needle in one case of mitral disease. The patient was immediately operated upon, and the catheter removed. The patient made an uneventful recovery.

This complication is easily avoided if the needle is removed together with the catheter when the catheter is caught by the needle.

In another case two catheters were introduced through two separate needles. One catheter was placed in the left ventricle, the other in the left atrium for a study of the pressure gradient across the mitral valves during exercise. The catheter in the left atrium slipped down into the left ventricle where the two catheters formed a knot. Operation as well as a commissurotomy were immediately performed with removal of the catheters. The recovery was uneventful.

For simultaneous pressure registration in the left atrium and the left ventricle we therefore recommend a catheter for the ventricle and a needle for the left atrium.

8. *Injection of Contrast Media Into the Wrong Place.*—In one case all contrast media were injected into the pericardial space. The patient experienced some pain afterward but had no sequelae otherwise. The investigation was repeated at a later date, and at the operation the pericardium had a normal appearance.

***The patient recovered after treatment with prolonged artificial ventilation and could walk around in the ward one month later. Then he suddenly died. Autopsy showed a fracture in the calcified valvular aortic stenosis, but the valvular function had not improved much due to the pathologic changes.**

In a second case the needle changed position during the injection and contrast media were injected into the left atrium, in the space between the two atria, and into the right atrium. The patient had no untoward reaction. At operation no defect or any abnormality could be palpated in the interatrial septum.

MINOR COMPLICATIONS

Seventy-three minor complications were observed in sixty-one cases or 36 per cent.

1. Pneumothorax.—Most common among these minor complications was a small pneumothorax. Most of these had an air space of only a few millimeters over the apex which was absorbed within a few days. Only on two occasions was it necessary to aspirate the air.

2. Pleural Effusion.—In twenty-six cases a small pleural effusion could be observed at x-ray investigation. It was not necessary to aspirate the fluid in any case as it was absorbed in a few days. No impairment of the pulmonary function was observed from this effusion.

3. Atelectasis.—Seven cases showed small atelectasis at x-ray investigation, after the anesthesia. In all cases the atelectasis disappeared after breathing exercises.

4. Hemoptysis.—Hemoptysis occurred in four cases.

5. Hematopericardium.—Hematopericardium was detected twice at the subsequent operation. There was no ill effect on the patient.

6. Hematoma.—A paravertebral hematoma occurred once and caused considerable pain. This patient had a bleeding tendency as well as a mitral stenosis.

SUMMARY

Left heart catheterization is an investigation which has much to offer in the accurate diagnosis and study of mitral and aortic valvular disease. It is a practical procedure which carries a reasonably low risk. However, left heart catheterization has been connected with some complications, and several of these can be avoided. Some complications cannot be avoided. Therefore we only advise a left heart catheterization where its diagnostic help is found necessary for the decision of an eventual surgical exploration. We believe a chest surgeon should perform the puncture and he should be equipped to perform a thoracotomy and defibrillation.

In our group of 150 cases of mitral stenosis major complications were observed in eleven cases or 7 per cent. No death occurred in this group and no patient had persistent sequelae.

In our seventeen cases of aortic valvular disease there were three major complications. In such cases with a small left atrium the puncture may be performed with the aid of fluoroscopy. We have had the most severe complications in this group, i.e. cardiac tamponade with ventricular fibrillation.

When angiocardiography is performed it is most important to have the patient well oxygenated during and after the anesthesia. The complications,

which have occurred in this group seem to be more related to the anesthesia than to the actual injection of contrast media.

The complication frequency could probably be lowered with a thinner needle. But, as we consider, it is essential to perform pressure measurements in the left ventricle and angiocardiography we will continue to use the technique outlined.

REFERENCES

1. Björk, V. O., Malmström, G., and Uggla, L. G.: Ann. Surg. **138**:718, 1953.
2. Björk, V. O., Malmström, G., and Uggla, L. G.: Am. Heart J. **47**:635, 1954.
3. Björk, V. O.: Acta Chir. scandinav. **107**:466, 1954.
4. Björk, V. O., Malmström, G., and Uggla, L. G.: Am. Heart J. **48**:8, 1954.
5. Björk, V. O., Blakemore, W. S., and Malmström, G.: Am. Heart J. **48**:197, 1954.
6. Björk, V. O., and Malmström, G.: Circulation Research **2**:424, 1954.
7. Björk, V. O., and Malmström, G.: Am. Heart J. **50**:303, 1955.
8. Björk, V. O., Kjellberg, S. R., Malmström, G., and Rudhe, U.: Am. Heart J. **49**:719, 1955.
9. Björk, V. O., and Malmström, G.: Am. Heart J. **50**:742, 1955.
10. Björk, V. O.: Le Poumon et le Coeur, Number 2, 1956.

STUDIES ON THE NATURE OF THE REPOLARIZATION PROCESS

XIX. Studies on the Mechanism of Ventricular Activity

Hubert Pipberger, M.D.,* Lois Schwartz, M.D., Rashid A. Massumi, M.D.,* and Myron Prinzmetal, M.D.

Los Angeles, Calif.

THE clinical significance of the T wave in representing the electrical recovery process of the ventricular myocardium is well known. This electrical phenomenon, however, has been the subject of much less basic research than other parts of the electrocardiogram. With the development, in recent years, of more reliable recording techniques and the introduction of an incubator in which animal experiments can be performed in a more physiologic medium, this study of the repolarization process of the heart muscle seemed justified.

Abundant controversy and confusion have developed over the direction of repolarization through the ventricular wall on the basis of polarity of the T wave. T polarity was studied by means of minute plunge electrodes recording simultaneously at selected depths in the ventricular walls. Moreover, the time course of the electrical recovery process was examined by comparing analogous points of the T wave in simultaneous records from the myocardial surface and the underlying subendocardium and from different surface points, and these results compared with the polarity of the T waves.

Experiments were designed also to study (a) the effect of local thermal changes upon adjacent and remote regions of the heart, (b) the effect of primary T-wave changes upon secondary ones by superimposing thermal changes upon left bundle branch block, and (c) the effect upon the T wave of ischemia due to chronic obstruction of coronary arteries.

LITERATURE

Prevailing theories on the electrical recovery of the heart muscle were derived from early and well-known experiments on muscle strip preparations. In such experiments, repolarization follows depolarization and has the same direction but opposite polarity (Fig. 1,*A*). Early electrocardiographers were

From the Institute for Medical Research, Cedars of Lebanon Hospital, and the Department of Medicine, University of California School of Medicine, Los Angeles.

Aided by Grants from the United States Public Health Service and the L. D. Beaumont Trust Fund.

Presented before the Second World Congress of Cardiology, Sept. 12 to 17, 1954, Washington, D. C.; The Third Annual Cardiac Conference, Nov. 11 to 13, 1954, Denver, Colo., and the 26th Annual Postgraduate Symposium on Heart Disease presented by San Francisco Heart Association, Oct. 5 to 7, 1955, San Francisco, Calif.

Received for publication March 29, 1956.

*Fellow, Los Angeles County Heart Association.

puzzled by the fact that most electrocardiograms showed the same polarity during the electrical activation and recovery process. Many theories tried to account for this apparent discrepancy between the electrocardiogram of the intact heart and that of the muscle strip preparation. The simplest and most popular explanation is that repolarization of the myocardium occurs in a direction reverse to that of depolarization (Fig. 1,*B*). The direction of depolarization from endocardium to epicardium is well documented, so it was assumed that the electrical recovery process was directed from epicardium to endocardium. Most authors quote Ashman[1,2] as reference for this assumption. However, he has stated only

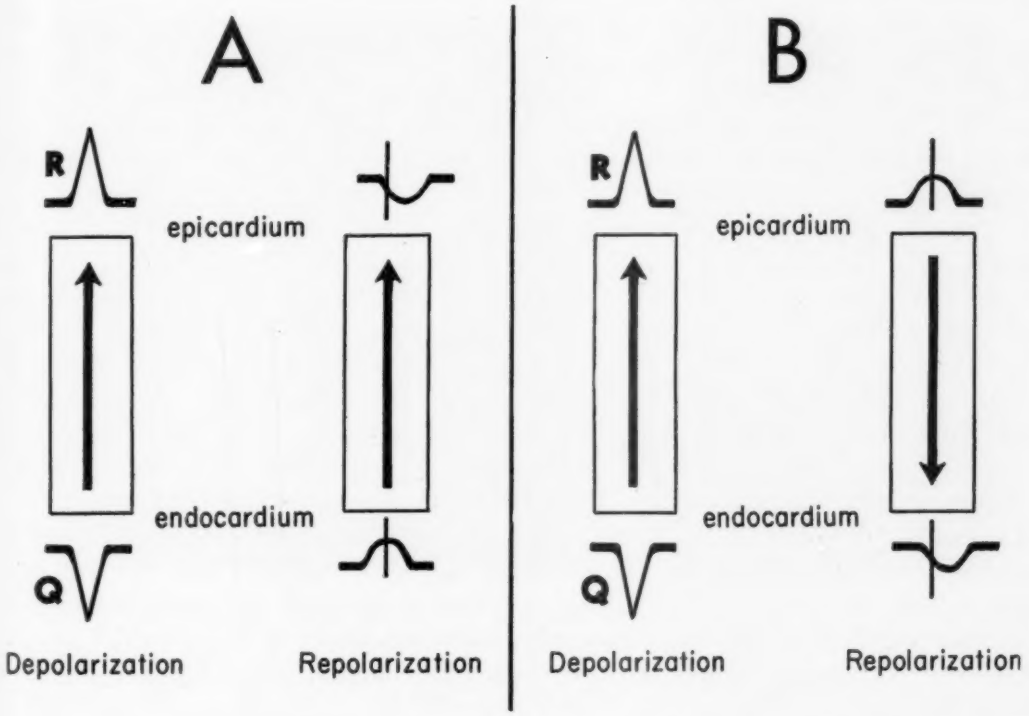


Fig. 1.—*A*, Findings on isolated muscle strip. Depolarization and repolarization have the same direction but opposite polarity. *B*, Modified muscle strip theory to account for the actual electrocardiographic findings. Depolarization and repolarization have opposite direction but same polarity. Thus repolarization was thought to proceed from epicardium to endocardium.

that this is one possible explanation for the fact that depolarization and repolarization have the same polarity in most electrocardiograms. Wilson and associates[3] stated, in 1931, that the observed phenomenon does not necessarily mean that the duration of the excited state is greater on the endocardial than on the epicardial surface. It might be due to differences between base and apex of the heart or between the basal and apical surface of the septum or between the epicardial and endocardial surfaces of the basal musculature. The concept of the ventricular gradient introduced by Wilson[4] and developed by Ashman[5-8] accounts for many possibilities by its definition as the net electrical effect of the differences in time course of the processes of depolarization and repolarization.

This is emphasized to avoid oversimplification in the explanation of the encountered phenomena.

Various causes have been considered responsible for changing the time course and the direction of repolarization. Grant and Estes[9] and Hellerstein and Liebow[10] consider a pressure difference between subendocardial and subepicardial layers to be responsible for a reversal of the repolarization process as compared to depolarization. This, however, has proved unlikely from the results of a recent investigation.[11] Massive changes of the pressure differences between inner and outer layers failed to change the ventricular gradient significantly, a change one would expect on the basis of this hypothesis.

As early as 1892 Bayliss and Starling[12] reported changes of the T wave in the electrocardiogram after application of heat or cold to the ventricular surfaces. Temperature effects on the repolarization process have been demonstrated subsequently by many investigators.[10,13-27] When heat is applied to the myocardium, increase in T positivity is observed; cold application causes an increase in T negativity.

Lepeschkin[27] was able to demonstrate that the temperature of the intraventricular blood was 1° C. lower than that in the inner part of the myocardial wall. At the same time, the temperature of the diaphragmatic surface of the heart was higher than that of the surface adjacent to the lungs. In other experiments, the same author[28] could abolish the ventricular gradient when Ringer's solution, which had exactly the same temperature as the intracavitary blood, was applied to the myocardial surface. This means that differences in temperature in different parts of the myocardium may be responsible for delay or acceleration of repolarization, thus giving rise to the normal ventricular gradient. Lepeschkin[27] concluded tentatively that the temperature difference between the trabecular portion of the subendocardium, which is cooled by the surrounding blood, and the warmer subepicardial portions of the same region, is responsible for the direction of normal repolarization and the polarity of the normal T wave. Others,[22,23,25] on the basis of their own experiments, gave support to this hypothesis.

Thus, although the exact time course of repolarization has never been clearly demonstrated, the available evidence seems to attribute a causative role to temperature differences in the genesis of the normal ventricular gradient.

The T wave is known to be more susceptible to changes than any other deflection of the electrocardiogram. Wilson[18] introduced the differentiation of primary and secondary changes. The former are independent, the latter are dependent on depolarization changes. The common denominator for the primary disturbances is thought to be a retardation of the electrical recovery in the involved myocardial region. Since the T forces in the uninvolved regions are not changed, the resulting main direction of the T points away from the site of the lesion. Negative T waves are supposed to be recorded over the zone of depolarization delay.

Bayley and La Due[29] performed total and subtotal coronary occlusion in animals and found that first the T wave became inverted over the involved region, then the S-T segment started to rise, and finally the T wave either dis-

appeared in or was in some cases visible on the positive side of the monophasic injury curve. T and S-T changes were reversible if the coronary blood flow had not been obstructed for too long a time. In the chronic stage, the T wave remained inverted over the infarcted area.

Wide interest has been evoked by whether primary T-wave changes can be superimposed on secondary ones.[16,25,30-38] This problem has clinical application in cases with bundle branch block complicated by myocardial infarction. All authors agree that superimposition is possible and rather frequent in clinical electrocardiography.

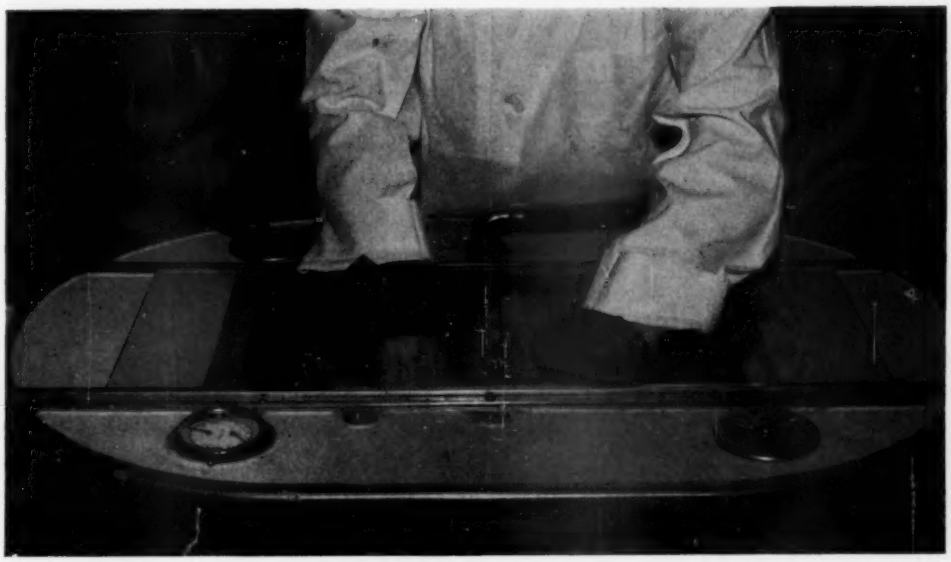


Fig. 2.—Infant incubator, modified to provide a near physiologic environment for open chest experiments in dogs.

MATERIAL AND METHODS

A total of forty-nine mongrel dogs was used in this study. The animals were anesthetized with pentobarbital sodium administered intravenously in doses averaging 25 to 30 mg. per kilogram of body weight. Wide exposure of the heart was accomplished by removing the third and fourth ribs bilaterally and retraction of the remaining chest wall. The pericardium was removed in most cases. An electric pump respirator maintained artificial respiration.

In all previous investigations, including our own, it was found that the T waves in areas of the heart exposed to room temperature were inverted. Attempts to control the temperature of the exposed heart by means of warm lamps, warm saline drips, and sprays were not entirely successful. Finally, an infant-size incubator (Fig. 2) was modified to maintain a constant temperature of 40° C. and a high humidity in order to provide an environment for these experiments approaching as closely as possible that of the closed chest. After an initial control electrocardiographic exploration taken at room temperature and con-

sisting of leads from the ventricular surfaces, intramural leads at selected depths in the myocardium, and leads from both cavities, each animal was placed in the incubator which was covered by glass plates to allow full vision of the animal's exposed heart. Holes in the glass cover were fitted with rubber cuffs allowing entry of the operator's forearms for free manipulation of the animal's heart and the electrodes, and at the same time preventing an air exchange between outside and inside.

In preliminary experiments, it was found that the animal had to be kept in this constant environment for at least one-half to one hour before the tracings from the ventricular surface showed stable T waves, a situation which was sometimes extremely difficult to achieve. During this period the originally inverted T waves gradually changed to upright. Records were taken as soon as the T waves showed no more changes in the milieu of the incubator.

Surface leads were taken with saline-soaked cotton-tipped silver wire electrodes. Similar electrodes were used for intracavitary leads. The silver wire was insulated up to the tip by polyethylene tubing which was passed through the right common carotid artery for leads from the left ventricle, and through the right jugular vein for catheterization of the right ventricle. The position in the cavity of the leading point of the electrode was ascertained by palpation after the chest was opened or after sacrificing the dog. Intramural and cavity leads were taken with sharp-tipped unipolar plunge electrodes which have been used extensively in this laboratory. Each electrode consisted of fine (0.020 gauge) tempered silver wire 3 to 4 cm. in length insulated to the tip by means of Glyptal cement (General Electric No. 1276). The tip was filed to a sharp point and chlorided by immersion in dilute hydrochloric acid through which an electric current was passed. The plunge electrodes were marked at intervals of 1 mm. in order to determine the depth of the leading point during the experiment. They were introduced into the myocardium at right angles to the surface. The thickness of the myocardial wall was determined in vivo by aspiration of blood into a syringe connected to a size 21 needle which was marked at 1 mm. intervals. The needle was inserted at right angles to the ventricular surface at the site where the plunge electrode had been introduced in the beginning of the experiment. This procedure was devised to avoid artefacts in measurements which occur when the thickness of the ventricular wall is determined post mortem after the myocardium has lost its tone.

In all experiments in which time measurements were made, a photographic-writing Sanborn twin-beam electrocardiograph was used. The frequency response was flat from 1 to 100 c.p.s. with a loss of 20 per cent amplitude at a frequency of 400 c.p.s. which assured accurate recording of the relatively slow T wave. The paper speed was 75 mm. per second allowing time measurements down to 0.004 second. In those experiments in which only polarity changes of the T wave were studied, a Sanborn Poly-Viso direct-writing electrocardiograph was used. The frequency response of this recorder is accurate up to 50 c.p.s. All leads taken were unipolar, using Wilson's central terminal as a reference pole. Additional experiments taken with contiguous bipolar electrodes proved to be unsatisfactory for the timing of the repolarization process due to the flatness of the T waves in most records.

1. *The Polarity of the T Wave.—*

A. *Surface Exploration.*—In surface explorations on the hearts of sixteen dogs in the incubator, 269 leads were taken from the left ventricle and 213 leads from the right ventricle. A minimum of eighteen leads was taken from each ventricle at specific locations over the anterior and posterior surfaces. Records with S-T shifts were discarded.

Results: The results of epicardial surface explorations on these dogs are shown in Table I. Positive T waves were found more frequently than negative ones, especially on the right ventricle. T negativity was found more frequently over the base than at any other surface location. However, areas with negative T waves were distributed quite irregularly, sometimes being very small and surrounded by areas of T positivity. No regular pattern of distribution could be established as there was much variation from one animal to another.

TABLE I. T POLARITY ON THE EPICARDIAL SURFACE IN THE INCUBATOR (SIXTEEN DOGS). THE MAJORITY OF T WAVES ARE POSITIVE. BY CONTRAST, WHEN THE HEART IS EXPOSED TO ROOM TEMPERATURE T WAVES FROM THE EXPOSED SURFACE ARE USUALLY INVERTED

	TOTAL NUMBER OF LEADS	T WAVE POSITIVE		T WAVE NEGATIVE		T WAVE BIPHASIC	
			%		%		%
Left ventricular surface	269	122	45.3	110	40.8	37	13.7
Right ventricular surface	213	163	76.5	25	11.7	25	11.7
Total	482	285	59.1	135	28.0	62	12.9

B. *Simultaneous Surface and Subendocardial Exploration.*—In ninety-eight instances on sixteen dogs, simultaneous leads were recorded from the ventricular surface and the underlying subendocardium on both ventricles.

Results: Concordant positive T waves were found in the majority of cases on both sides of the ventricular wall, more often, however, on the right ventricle than on the left (Fig. 3) (Table II). Here again, there was no definite pattern of polarity distribution.

TABLE II. T POLARITY IN SIMULTANEOUS LEADS FROM THE EPICARDIAL SURFACE AND THE UNDERLYING SUBENDOCARDIUM IN THE INCUBATOR (ELEVEN DOGS). IN THE MAJORITY, T WAVES WERE POSITIVE FROM BOTH SURFACE AND SUBENDOCARDIUM

	TOTAL NUMBER OF LEADS	SURF. POS. SUBENDO. POS.		SURF. NEG. SUBENDO. POS.		SURF. NEG. SUBENDO. NEG.		SURF. BIPHASIC SUBENDO. POS.	
			%		%		%		%
Left ventricle	57	27	47.3	25	43.8	0	0	5	8.7
Right ventricle	41	29	70.7	7	17.9	1	2.4	4	9.7
Total	98	56	57.1	32	32.7	1	1.0	9	9.2

C. *Close-Chest Experiments.*—In order to compare the polarity of T waves from the open-chest dog in the incubator with those obtained from the close-chest dog, intracavitary leads were taken in nine dogs before the chest was opened, as described by Hellerstein and Liebow.[10] Each of these leads was recorded simultaneously with a subcutaneous lead taken from the overlying chest wall. The left ventricle was investigated in six of the dogs with an intracavitary electrode passed through the right common carotid artery, and the right ventricle in three dogs by means of an electrode inserted through the right jugular vein.

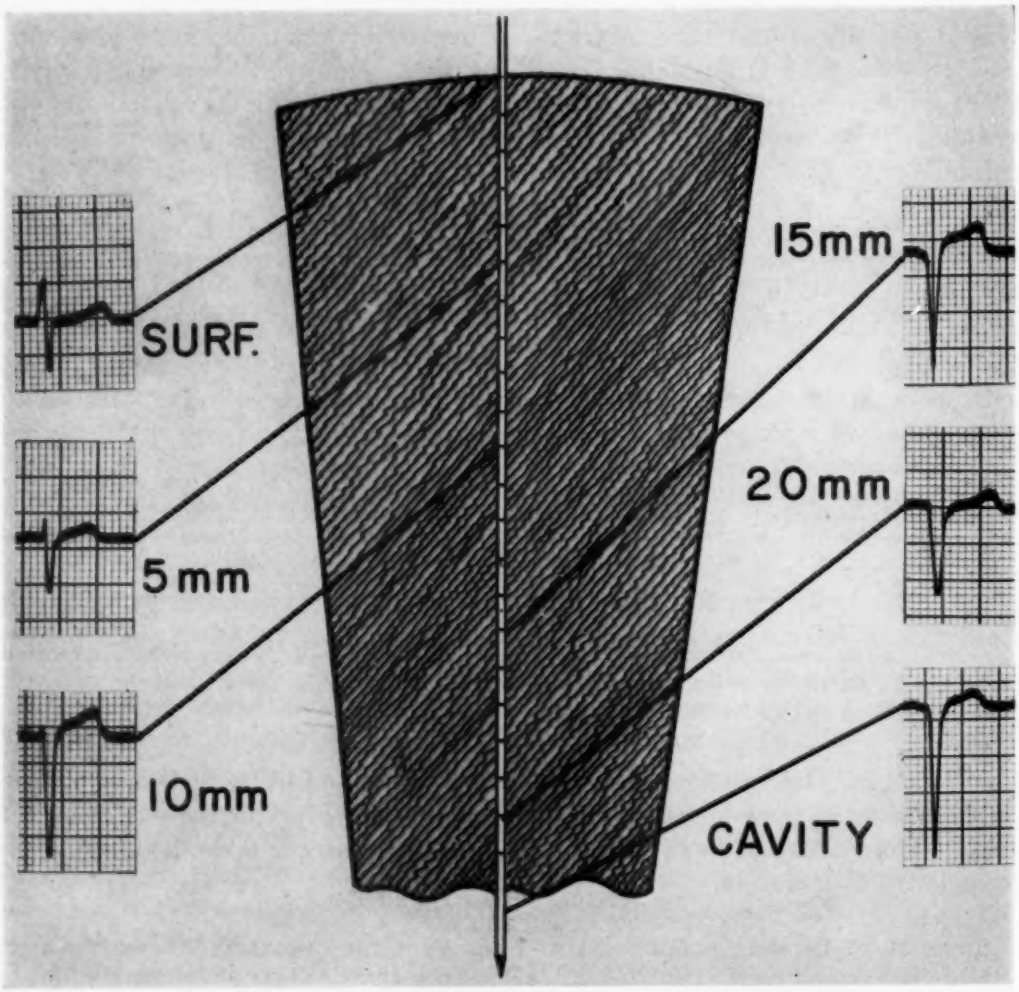


Fig. 3.—Actual findings of T polarity in most cases at selected depths in the ventricular wall when recorded in the incubator. In this instance T waves from cavity, intramural, and epicardial leads are all positive.

Results: In the six dogs in which the left ventricle was catheterized, positive T waves were found in the intracavitary and subcutaneous tracings in all instances (Fig. 4). Similarly, positive T waves from the cavity as well as subcutaneously over the right ventricle were found in the three dogs in which the right chambers were catheterized (Table III).

2. *The Time Course of Repolarization.*—

A. *Time Correlation of Surface and Subendocardial T Wave.*—For the purpose of studying the time course of repolarization through the ventricular wall, simultaneous records were taken from the ventricular surface and the underlying subendocardial region in sixty-nine instances from both ventricles of eleven dogs. These experiments were performed usually at ten different locations on each ventricle. A plunge electrode was inserted into the myocardium until the resistance of the endocardium was felt and then withdrawn 1 to 2 mm. A surface electrode was

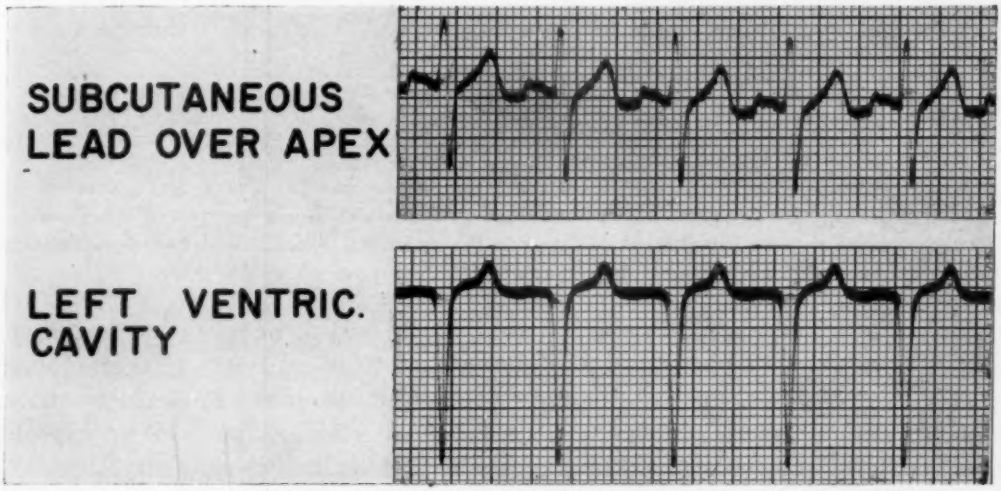


Fig. 4.—Close-chest dog. Concordant T-wave polarity recorded from left ventricular cavity and overlying subcutaneous tissue.

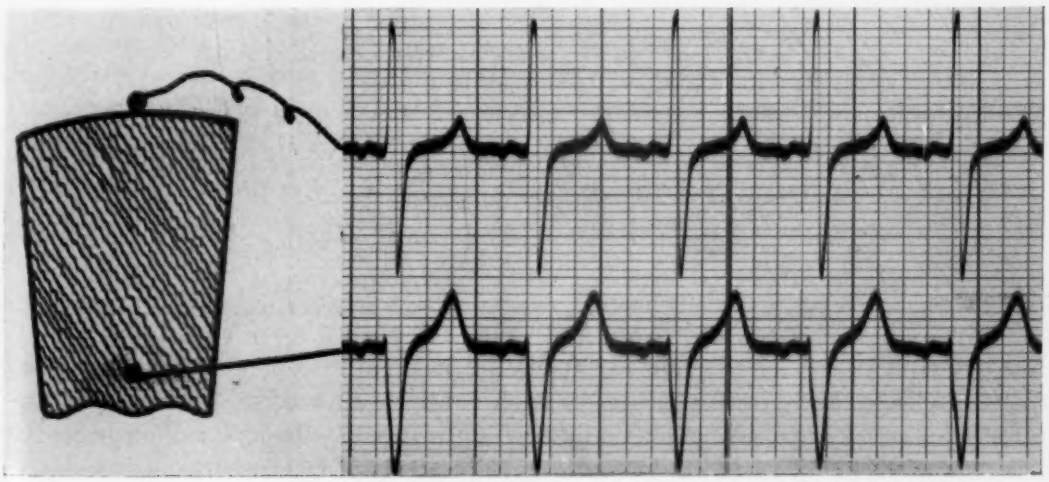


Fig. 5.—Simultaneous leads from left ventricular surface and underlying subendocardium in the incubator. The T apex from the subendocardium precedes that from the epicardium.

placed on the overlying epicardium so that a line connecting the two electrodes would have been perpendicular to the epicardial and endocardial surfaces. The apex of the T wave was found to be most appropriate for a common reference in all T-wave determinations. The beginning and end of the wave are in most cases less sharply outlined due to the relatively slow time course of the electrical recovery process, whereas the transition from the slower first part of the wave to the much faster second part can be determined in almost all cases with satisfactory accuracy. This

TABLE III. T POLARITY IN SIMULTANEOUS LEADS FROM THE VENTRICULAR CAVITY AND THE OVERLYING SUBCUTANEOUS TISSUE. CHEST NOT OPENED (NINE DOGS). T WAVES WERE UPRIGHT FROM CAVITY AND SUBCUTANEOUS LEADS THROUGHOUT

	CAVITY LEAD		SUBCUTANEOUS LEAD	
	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
Left ventricle	6	0	6	0
Right ventricle	3	0	3	0
Total	9	0	9	0

advantage of the apex of the T wave over the beginning or the end in time determinations was outlined previously by Lepeschkin and Surawicz.[39] All leads in which the apex of the T was not sharply outlined were excluded from this study. Furthermore, all leads with S-T deviations due to injury were discarded because injury may change the course of repolarization.

Results: The subendocardial T apex was found to be earlier than the epicardial T apex with a mean time difference of 0.006 ± 0.005 second (Fig. 5) (Table IV). From the distribution curve of the results, it was calculated that in 86.5 per cent of all measurements, the subendocardial T apex can be expected to precede the surface T apex, the reverse being true in 13.5 per cent.

TABLE IV. TIME DIFFERENCE BETWEEN APICES OF T WAVES FROM SURFACE AND SUBENDOCARDIUM (BOTH VENTRICLES). THIS STRONGLY SUGGESTS THAT THE REPOLARIZATION PROCESS PROCEEDS FROM ENDOCARDIUM TO EPICARDIUM

	SUBENDO.	SURFACE	SIMULTANEOUS
Earlier in:	59	4	6

Total: 69

Mean time difference	0.006 sec.
Standard deviation	0.005 sec.
Standard error	0.001 sec.
t	9.07
P	0.001

A comparison of the findings from the right and left ventricles and from basal, middle, and apical portions of each ventricle showed no difference of statistical significance, indicating that the T apex in the subendocardium precedes the epicardial T apex similarly in different regions of the ventricles.

B. *Time Correlation of Right and Left Ventricular Surface T Waves.*—For the purpose of studying the time relations of the T waves from corresponding areas of the right and left ventricular surfaces, simultaneous leads were taken from apical, middle, and basal surface locations of the two ventricles anteriorly, laterally, and posteriorly. Thirty experiments were done on eight dogs.

Results: The T apices of the right ventricle preceded those from the left ventricle by a mean time difference of 0.005 ± 0.011 second (Table V). The range of distribution, however, was rather large as indicated by the value of the standard deviation.

TABLE V. TIME DIFFERENCE OF T APEX BETWEEN RIGHT AND LEFT VENTRICULAR SURFACES. THE APEX OF THE T WAVE FROM THE RIGHT VENTRICULAR SURFACE IS EARLIER THAN THAT FROM THE LEFT

	RIGHT VENT.	LEFT VENT.	SIMULTANEOUS
T apex earlier on:			
Basal portion	5	1	3
Middle portion	7	3	0
Apical portion	6	3	2
Total	18	7	5

Mean time difference	0.005 sec.
Standard deviation	0.011 sec.
Standard error	0.002 sec.
t	2.32
P	0.02–0.05

C. *Time Correlation of Apical and Basal Surface T Waves.*—In twenty experiments on eight dogs, simultaneous leads were taken from the apex and base of each ventricle in order to study the time course of repolarization on these two surface regions of each ventricle.

Results: The time difference between the peak of the T wave at the apex and that at the base was 0.0 ± 0.007 second (Table VI). No significant difference was found between the figures from the right and left ventricles. The mean time differences indicated that the T apices from the base and apex of each ventricle occurred simultaneously.

D. *Correlation of T-Wave Polarity and Repolarization Time Course.*—In order to determine whether T polarity could be considered to be indicative of the time course of repolarization in these experiments, the time difference in seconds between the epicardial and subendocardial T apices was plotted against the difference in magnitude of polarity of the same T waves. Seventy-five and four-tenths per cent of the plotted values fell in an angular range of 77 per cent with an extremely wide scatter. Thus, the time course of repolarization had no demonstrable relationship to the difference in polarity between the epicardial and subendocardial T waves. Polarity and time relationships varied independently.

TABLE VI. TIME DIFFERENCE OF T APEX BETWEEN APICAL AND BASAL SURFACES OF THE LEFT AND RIGHT VENTRICLE. THIS DIFFERENCE IS NOT SIGNIFICANT

	APEX	BASE	SIMULTANEOUS
T apex earlier on:			
Left ventricular surface	5	6	2
Right ventricular surface	1	3	3
Total	6	9	5

Mean time difference	0.0 sec.
Standard deviation	0.007 sec.
Standard error	0.002 sec.
t	0.0
P	0.90

3. *Influence of Thermal Changes on the Repolarization Process.*—

Because our preliminary work revealed that the application of hot or cold saline to the myocardial surface had inconsistent effects upon the T waves recorded from the site of application and from the opposite surface of the ventricular wall, it was felt that the size of the area heated or cooled and the temperature of the saline used had a quantitative influence upon the induced T changes. For this reason, graded amounts of saline from ¼ c.c. to 20 c.c. were used in a stepwise fashion upon the area subjected to thermal change, and the temperature of the saline was kept constant for a given experiment. In different experiments, the temperature of warm saline ranged from 43 to 46° C., and that of the cold saline from 15 to 30° C. Temperature changes on the endocardial surface were induced by injecting cold or warm saline into the cavity. This was done by introducing intracavitary catheters through the venous route from the right jugular vein or from the left pulmonary veins. Cold saline was injected in an amount ranging from 10 c.c. to 25 c.c., warm saline from 50 c.c. to 60 c.c. The temperature of the injected fluid was the same as that used for epicardial application.

A. *Effect of Cold and Heat Applied to the Ventricular Surface.*—In ten dogs, cold saline was applied to the ventricular surface in graded amounts from ¼ to 20 c.c. After each step, a sufficient time interval was allowed for the T wave to return to the control level. Simultaneous leads were recorded from the surface at the site of change and from the opposite side of the ventricular wall, either the cavity or subendocardial region, and sometimes from the opposite side of the heart. In similar fashion, warm saline was applied to the epicardial surface in fourteen dogs.

Results:

Effect of cold. The application of cold saline to the ventricular surface resulted in an increased negativity of the T wave. This was observed in originally positive and negative T waves. The amount of change in polarity corresponded largely to the quantity of cold saline used (Fig. 6). Changes opposite in polarity to those on the surface were expected in the underlying subendocardial lead. These changes, however, were very small or absent when small amounts of cold saline were used. With larger amounts, and a resultant increase in the area cooled, distinct reciprocal polarity changes in the subendocardial T wave were seen. The magnitude of these subendocardial changes was always much less than those at the site of cold application as shown in Fig. 6 where the approximate relation of the changes between the surface and the subendocardium was 10:1. Cooling increased the total duration of activity as indicated by a prolonged Q-T interval. The time difference between surface T apex and the subendocardial T apex changed very little and never fell outside a range of 0.1 second above the control level. The change in this time difference did not follow the change in polarity of the surface T.

Effect of heat. Application of warm saline to the epicardial surface caused an increase in T positivity at the site of application (Fig. 7). Similar to the cold experiments, the changes of the T wave corresponded very closely to the amount of saline used and the size of the area heated. The findings in the subendocardial tracings again showed little or no changes with small amounts.

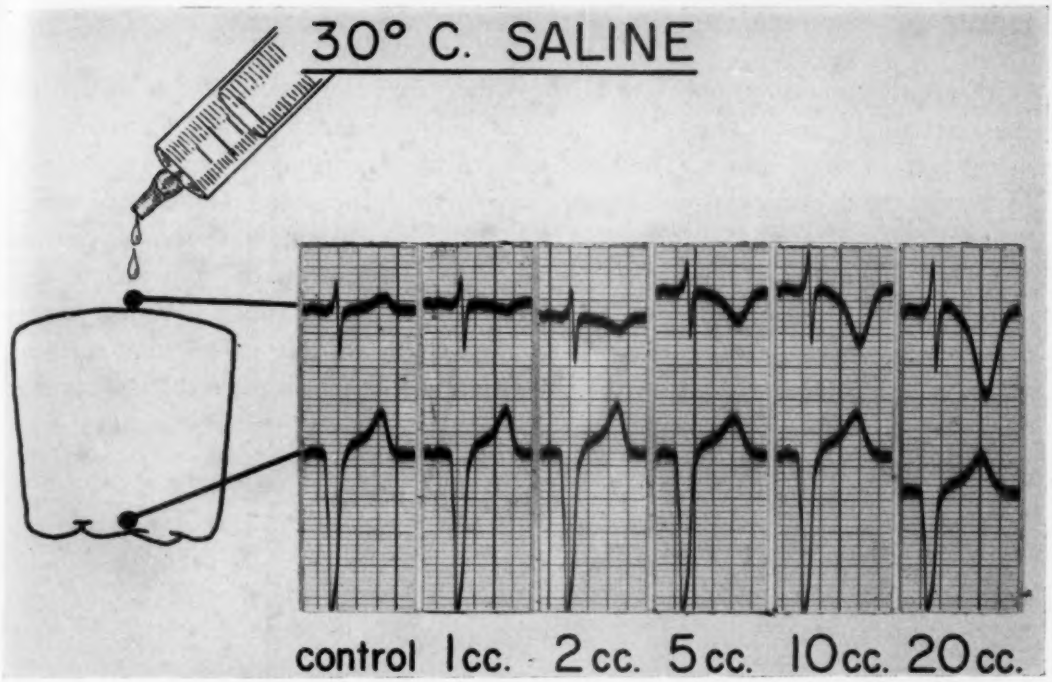


Fig. 6.—Application of cold saline in graded amounts to the epicardial surface. Simultaneous leads from surface at site of application and from underlying subendocardium. T negativity increases at the site of application with larger amounts of cold saline. Smaller opposite polarity changes are seen in the subendocardial leads. With small amounts, change of the subendocardial T wave is imperceptible.

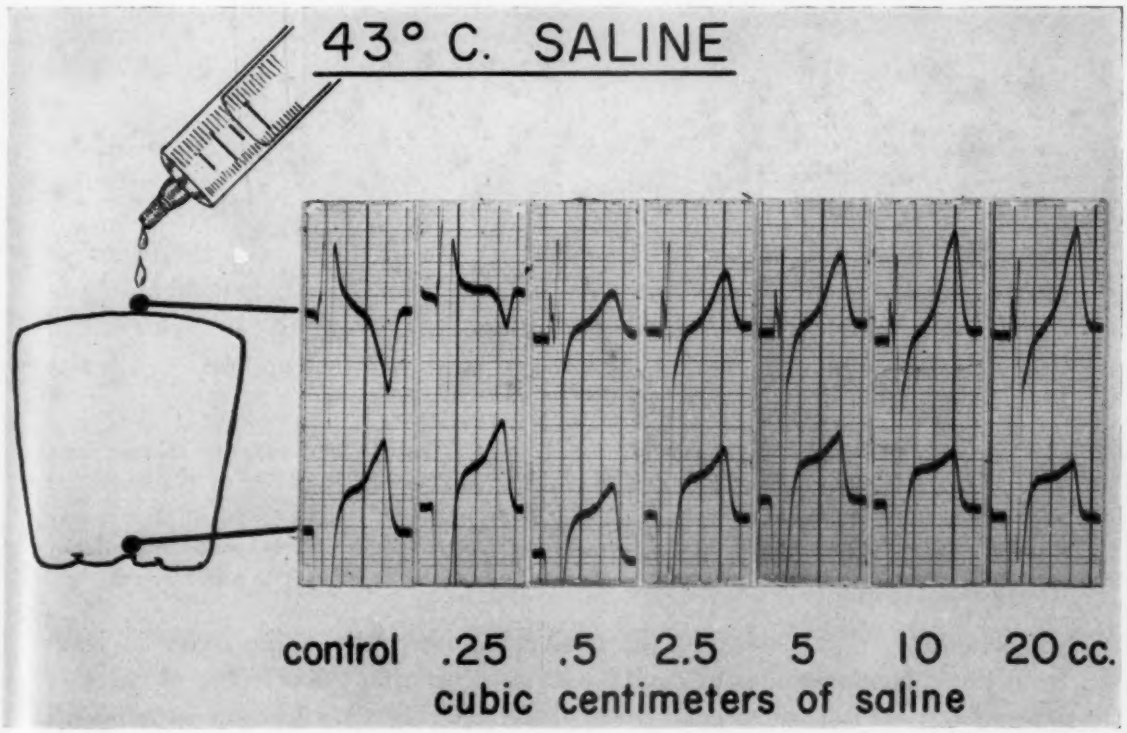


Fig. 7.—Application of warm saline in graded amounts to the epicardial surface. Simultaneous leads from surface at site of application and from underlying subendocardium. T positivity increases at the site of application with larger amounts of warm saline. Smaller opposite polarity changes are seen in the subendocardial leads. With small amounts, the changes in the subendocardium are extremely small or imperceptible.

With greater amounts, opposite changes increased but never to the extent of the surface changes. The Q-T interval was shortened, as a rule, but remained unchanged in a few cases. The time delay of the epicardial T apex as compared to that in the subendocardium became smaller with increasing amounts of warm saline used. The surface preceded the subendocardium, however, in only a very few instances. These changes in time relationship did not follow the conspicuous alterations of the T polarity in a linear fashion. When larger amounts of warm or cold saline were applied to the left ventricular surface, and leads were taken from the opposite side of the heart on the right ventricular

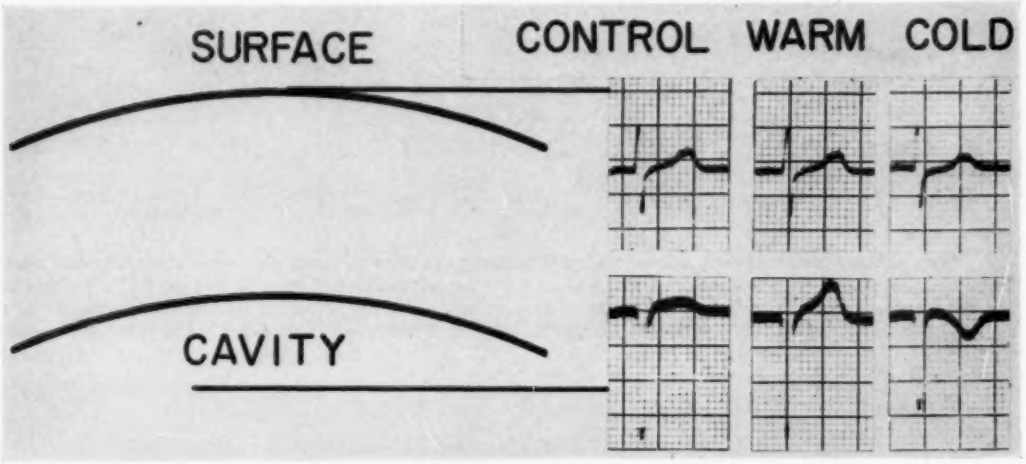


Fig. 8.—Injection of warm and cold saline in left ventricular cavity. Simultaneous leads from left ventricular cavity and surface. Note the marked T-wave changes in the cavity with very little change of the surface T wave.

surface, the T-wave changes there were similar to those found in the subendocardium underneath the site of thermal changes. In the same fashion, application of large amounts of heat or cold to the right ventricular surface resulted in reciprocal T-wave changes on the left ventricular surface opposite to the site of application.

B. *Effect of Injecting Warm and Cold Saline Into the Ventricular Cavity.*—In thirteen dogs, warm or cold saline was injected into the left or right ventricular cavity. Due to the immediate mixing of blood with the injected saline, larger amounts of saline had to be used in these experiments than in the previous ones. For this reason, and also because the injected saline immediately entered the coronary circulation, graded changes were much more difficult to produce.

Results: Warm saline in the cavity increased the T positivity in leads from the subendocardium or cavity with a concomitant shortening of the Q-T interval. Cold saline caused the opposite effect (Fig. 8). In some experiments T-wave changes occurred in the cavity and the subendocardial layers but an opposite effect on T waves from the epicardial leads was absent or imperceptible.

In the majority of experiments, however, an opposite effect was clearly demonstrated. This opposite effect again was always quantitatively smaller than the T changes at the site of thermal changes.

C. *Effect of Injection of Cold Saline Intramurally.*—In one dog, ¼ c.c. of cold saline was injected by means of a needle and syringe into the middle portion of the left ventricular wall. Simultaneous leads were taken from the left cavity, the epicardial surface, and from the site of cold injection.

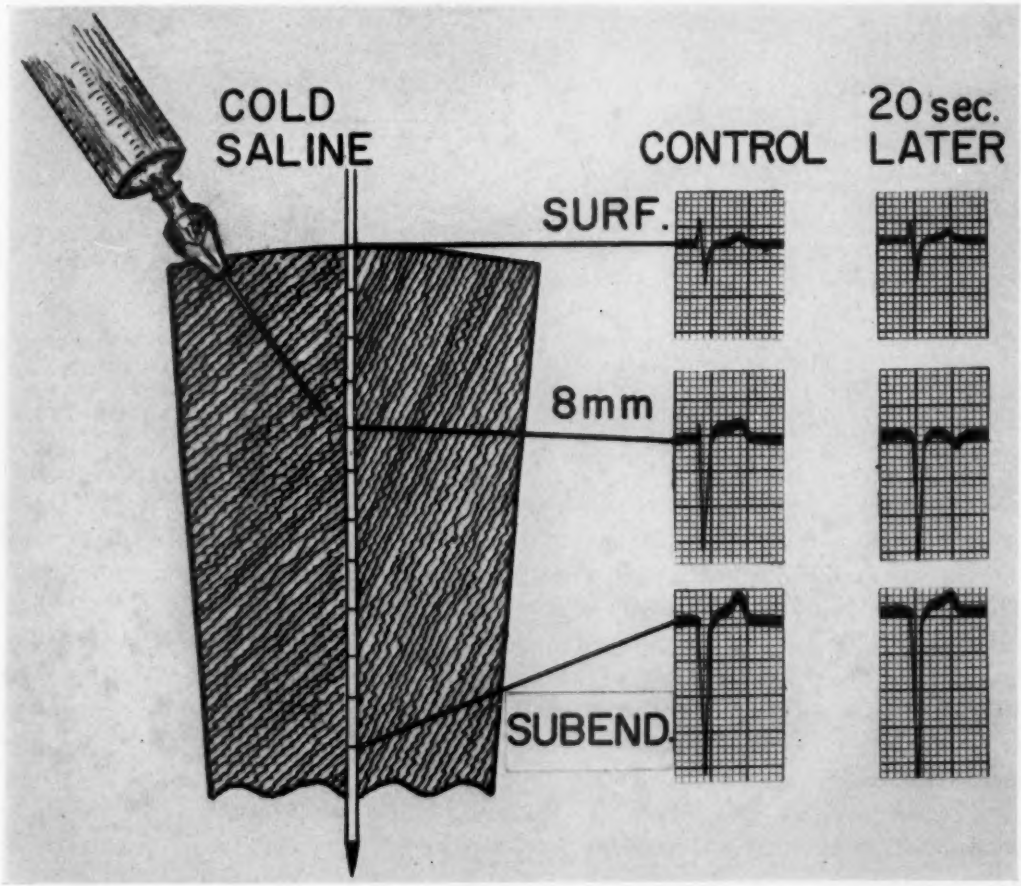


Fig. 9.—Midmural injection of ¼ c.c. cold saline. Simultaneous records from site of injection and from overlying surface and underlying subendocardium. Definite T-wave change at site of cooling with no reciprocal polarity changes in the other leads.

Results: At the site of injection in the wall, the T wave became inverted while the other two leads only a few millimeters away showed almost no discernible T changes (Fig. 9).

D. *Effect of Minute Thermal Changes Applied to the Ventricular Surface.*—In an experiment previously performed in this laboratory[54] three cotton-tipped electrodes were placed on the epicardial surface of the heart 1 to 2 mm. apart. After taking a control tracing, one electrode was heated and another was cooled, the third being kept at room temperature.

Results: The heated and cooled electrode recorded the same T-wave changes as previously described; the electrode at room temperature recorded an unchanged T wave. Thus, thermal changes could be restricted to very small areas without necessarily affecting adjacent or distant leads.

E. *Effect of Thermal Changes on the Human Ventricular Surface.*—While doing electrocardiographic studies on the exposed human heart,[55] warm and cold saline were applied to the epicardial surface in one case.

Results: The T-wave changes were similar to those described in the dogs (Fig. 10).

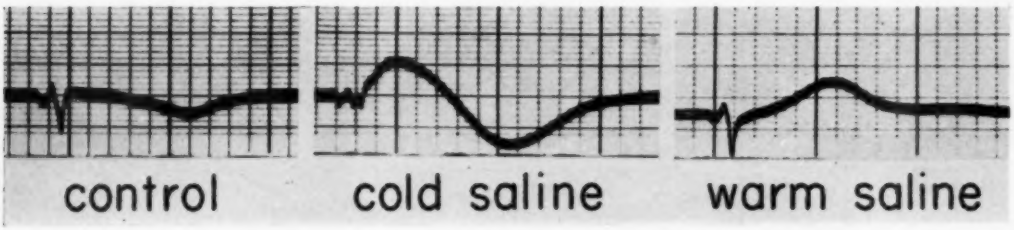


Fig. 10.—Left ventricular surface leads from human heart exposed in the course of chest surgery. Application of cold saline increases T negativity; warm saline, T positivity.

4. *Ischemic T-Wave Changes.*—

In order to study the T-wave changes induced by ischemia, the second left ventricular branch of the anterior descending coronary artery was ligated in each of four dogs, and the main trunk of the anterior descending artery at the junction of the upper and middle third was ligated in each of four dogs. The size of the region deprived of bood supply was larger in the group with ligation of the main trunk than in the group with occlusion of the left ventricular branch. Surface explorations of the infarcted hearts were performed in the incubator after an interval of from one to fifty-two days following the coronary artery occlusion, so that records were obtained of the T-wave changes in different stages.

To investigate the effect of further changes superimposed on ischemic primary T-wave changes, warm saline was applied to the areas of surface T inversion due to ischemia.

Results: In six cases, when the chest was reopened and the animal placed in the incubator, the T waves in leads from the ventricular surface were positive over normal and infarcted areas. In these same animals, however, some small areas of T negativity were found at the margins of the infarctions. In two other animals, positive and negative T waves were observed over normal and necrotic areas without a definite relationship to the infarct. Intramural leads beneath the area of T negativity recorded negative T waves only in the outer layers (Fig. 11). Application of hot saline to the areas of T negativity reversed the T wave to a positive position in all but one case (Fig. 12). The appearance of T-wave alterations due to heat in these experiments demonstrated the presence of live tissue in the infarcted region.

5. *The Influence of Primary T-wave Changes on Secondary Ones.*—

The effect of primary T-wave changes due to heat upon secondary T-wave alterations associated with left bundle branch block was studied in five dogs by cutting the left bundle branch with a knife, using the left ventricular ap-

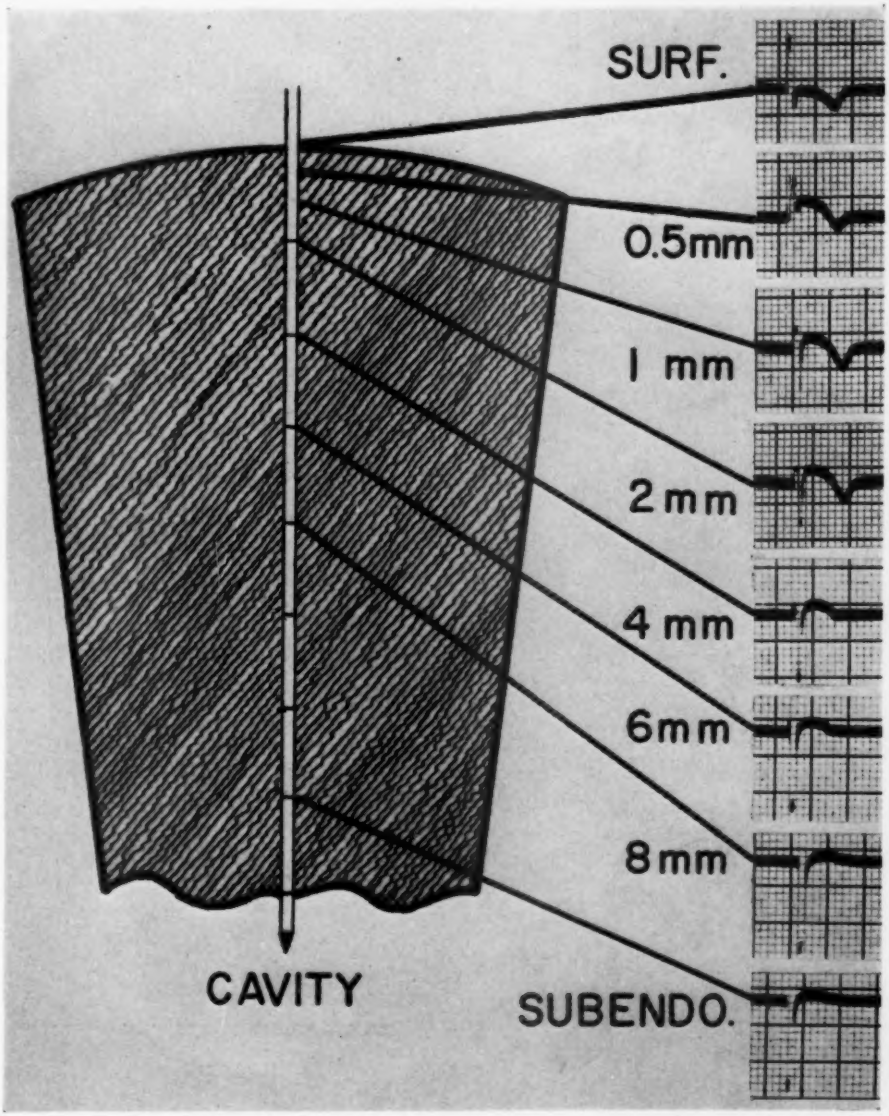


Fig. 11.—Intramural recordings from dog in incubator. Leads taken at the margin of old infarct. T negativity restricted to the outer layers.

proach. With similar purpose, heat was applied to the left ventricular surface in two dogs during the production of premature ventricular contractions by means of mechanical stimulation of one of the ventricles.

Results: In the five dogs in which the left bundle of His was cut, the application of warm saline to the epicardial surface of the heart caused the same

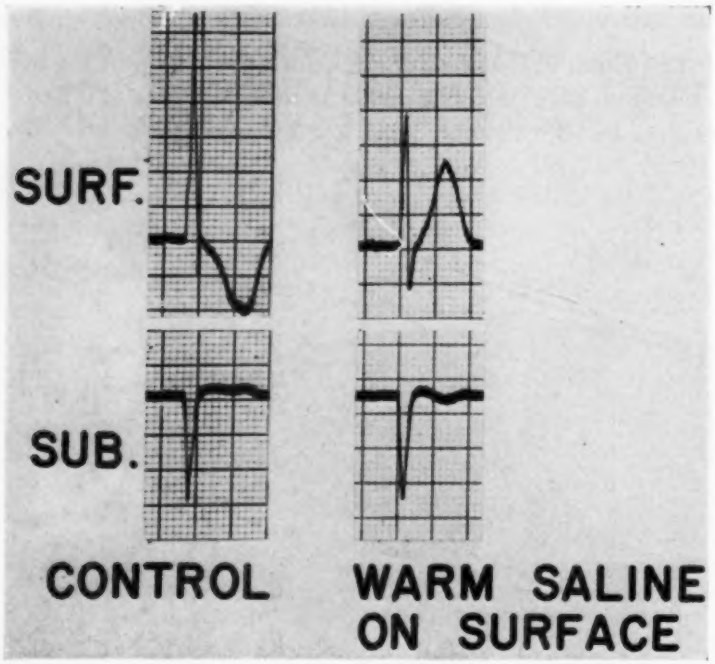


Fig. 12.—Effect of warm saline on the negative T wave at the margin of old infarct. Simultaneous leads from the epicardial surface and the underlying subendocardium. Note that the T wave inverted by "ischemia" becomes upright.

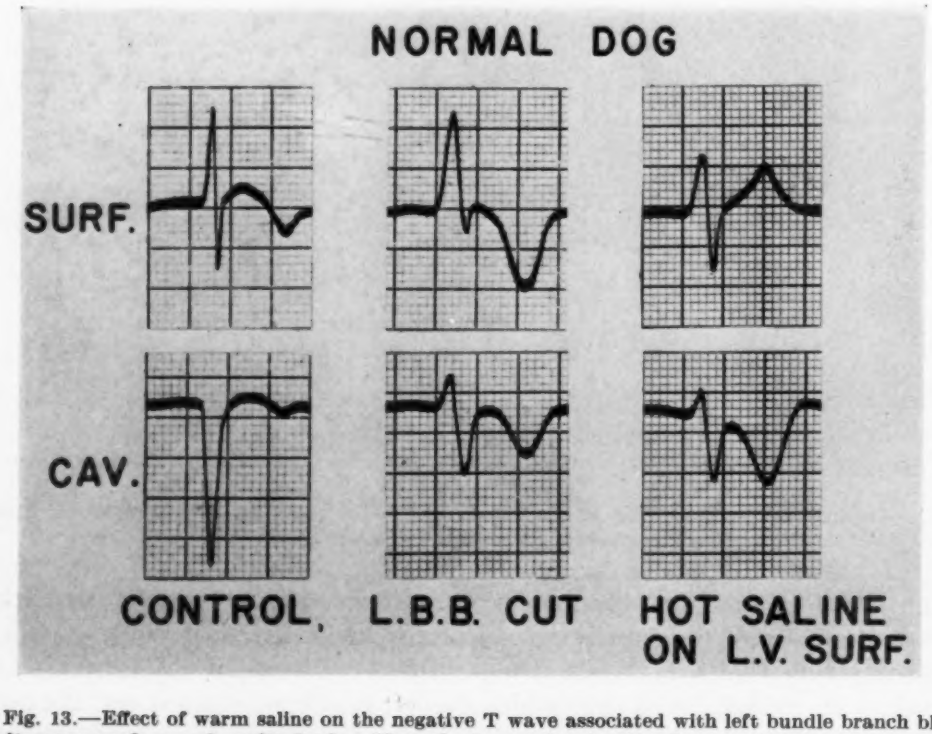


Fig. 13.—Effect of warm saline on the negative T wave associated with left bundle branch block. Simultaneous surface and cavity leads. Note the inverted epicardial T wave becomes positive.

changes as in the experiments on normal hearts (Fig. 13). The deeply inverted T waves associated with bundle branch block could be reversed to positivity by application of warm saline. Analogous results were seen when premature ventricular contractions were induced by mechanical stimuli to the heart's surface. The secondary T-wave changes of these beats were altered by heat in the same way as in left bundle branch block.

DISCUSSION

1. *The Polarity of the T Wave.*—Reciprocity of the T-wave polarity could not be demonstrated in the majority of those experiments in which epicardial leads were taken simultaneously with leads from the underlying subendocardium or cavity. In most of the records, the T wave was positive on both sides of the ventricular wall. Opposite polarity on opposing wall surfaces was found, however, in the majority of records taken at room temperature, the T being negative on the surface and positive in the subendocardium or in the cavity. The difference in these findings can be explained by the exposure of the surface of the heart to room temperature. The cooling effect of the room air inverts the surface T waves. This was prevented in our experiments by the introduction of the incubator which approaches close-chest conditions, although it cannot be assumed to present such conditions exactly.

The T-polarity distribution on the ventricular surfaces when recorded in the incubator corresponded very closely to the findings of Groedel and Borchardt.[42] No reciprocal T polarity could be demonstrated in the experiments on close-chest dogs where simultaneous leads were taken from the ventricular cavities and the overlying subcutaneous tissue. In all these experiments the T was positive in both leads.

Hellerstein and Liebow[10] reported different results in analogous studies on ten dogs with leads from the left ventricular cavity and the subcutaneous region overlying the apex of the heart. They found reciprocal T polarity in all instances, the T waves from the cavity being negative. We are unable to explain this discrepancy in findings. Our results seem to indicate, however, that cavity T waves recorded from close-chest animals are not necessarily negative or reciprocal to those recorded from the chest wall. This agrees with the findings made in the incubator on open-chest dogs.

Catheterization studies by numerous investigators[43-55] have included results of intracavitary recordings in human hearts. Most of these reports deal with records taken from the right ventricle. The number of normal subjects is rather small. In the majority of cases, the T wave was negative in both chambers of the heart but not necessarily so. This discrepancy with our findings may be due to the difference between human and experimental subjects.

Previously it was assumed that any given segment of the ventricular wall extending from endocardium to epicardium behaved electrically in a fashion similar to that of an isolated muscle strip (Fig. 14,*A*). Electrical processes in such a segment were thought to follow roughly the same direction as those in the isolated strip, and leads taken from each side of the wall, just as in the isolated strip, presumably recorded only the flow of current in between. The line

of transition between the positive and negative electrical field, the dipole layer, was described previously as proceeding from epicardium to endocardium during electrical recovery, giving rise to a positive T deflection on the epicardial surface and a negative T wave in the cavity. Our findings of concomitant positive T polarity on both sides of the ventricular wall in the majority of cases are not compatible with this concept.

Although surface T negativity was found more frequently over the basal region, the most striking finding was a complete lack of uniformity in the surface polarity distribution from one animal to another.

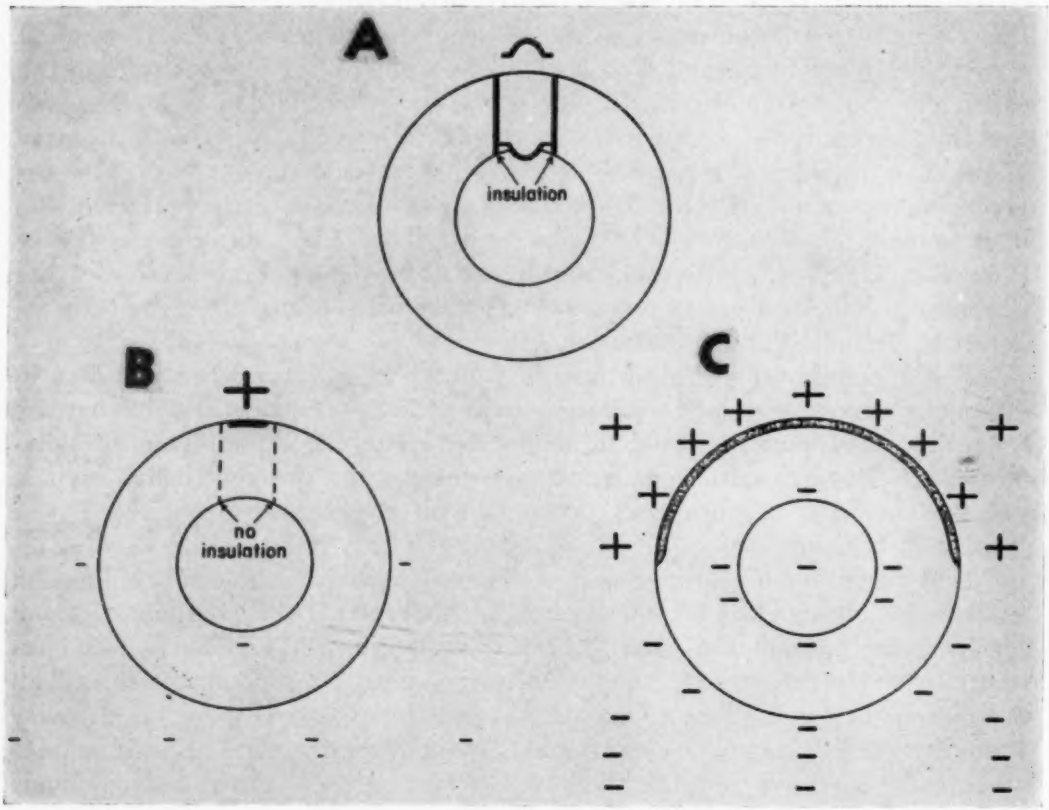


Fig. 14.—Simplified diagrammatic representation of cross section of ventricle. *A*, According to concepts based on electrical behavior of an isolated muscle strip, a segment of wall from epicardium to endocardium would behave independently of rest of wall as though insulated from it. The epicardial and endocardial T waves would have reciprocal polarity and equal magnitude. *B*, Since no insulation exists any small change in one region, as indicated on the surface by the plus sign, must be balanced by equal opposite polarity changes in all other regions. The total sum of charges has to be equal zero. If the primary change is restricted to a small region, the opposite polarity changes may be too small in adjacent or remote regions to be detectable. *C*, Conversely, a change extending over a large area is balanced by larger opposite polarity changes which are easily seen in leads from adjacent and remote regions. The total sum of charges has to equal zero again.

In any electrical system, including that of the heart, the positive and negative charges must be equal. Demarcation of positive and negative zones, however, was not demonstrable in the above experiments using unipolar leads in the arrangement described. Our findings indicate that summated electrical

fields, rather than potentials from isolated muscle segments, become demonstrable as long as the heart is in action as a whole. These fields, however, seem to be very irregular and cannot be defined in the same fashion as on the body surface. A differentiation between summated electrical events from the heart as a whole and electrical effects from the site of leading has proved extremely difficult.[56] Thus, we assume that, in the described leads, summated electrical fields as well as local potentials are effective rather than the latter alone.

2. *The Time Course of Repolarization.*—

Studies about the time course of repolarization on the basis of simultaneously recorded T waves from different regions of myocardium have not been reported previously. In our investigations, the apex of the T wave was used for all measurements, as previously done by Lepeschkin.[39] Besides the technical advantage of this reference point for our purposes, we noted in all our records that this point showed different time relations in leads from different areas of the heart which suggests that the apex of the T wave may represent a local repolarization process. We are not able to state at this time if this point which represents the transition from a slow to a faster portion of the T wave is analogous to the intrinsicoid deflection of the depolarization process or any other process.

In the great majority of all records taken, there was a definite time delay in the repolarization of the epicardial surface as compared to the underlying subendocardium. The time delay seemed to be similar in all regions of the heart. According to the distribution curve of our findings, however, it can be expected that in 13.5 per cent of the total, the repolarization process may be directed from the surface to the subendocardium. This rather limited difference between the time course of depolarization and repolarization in an endocardial-epicardial direction cannot explain, however, the net sum of differences of the whole heart, i.e., the ventricular gradient.

The most striking finding was that the time course of repolarization showed no correlation to the polarity of the T wave. In previous studies when no time measurements were made, the polarity of the T wave was taken as a sign of the direction of the repolarization process.[10] In the light of time measurements, this assumption appears unlikely. Polarity and time course, although related to each other theoretically, are obviously able to vary independently under the circumstances of these experiments.

The time correlation between T apices from corresponding areas of the right and left ventricular surface showed a statistically significant delay of the left chamber as compared to the right. Presumably, the lesser thickness of the right ventricular wall is a major factor responsible for the earlier termination of repolarization of the right chamber. No significant difference in time could be observed when the T apex was studied in simultaneous surface leads from the apex and base of both ventricles. Since depolarization of the apex precedes that of the base, and repolarization appears to be simultaneous in apex and base, a difference in the duration of activation between these two regions seems to exist, as was postulated by Schaefer.[57] Due to the small number of these experiments, however, we can draw this conclusion only tentatively, and it should be

confirmed by additional experiments. This difference in the duration of activation could be a major factor in the genesis of the normal ventricular gradient. It should be emphasized, however, that the ventricular gradient represents the net electrical sum of the differences in the time course between depolarization and repolarization. Other factors may contribute to this summated effect as was pointed out by Wilson.[3]

3. *Influence of Thermal Changes on the Repolarization Process.*—

Many investigators[13-27] have shown that the polarity of the T wave can be changed at will by changing the temperature of the heart. Cold induces an increase in T negativity, and heat an increase in T positivity, probably as a result of unknown biochemical changes in the myocardial tissue. We attempted to quantitate these changes on the ventricular surface. The degree of alteration of the T wave was dependent on the amount of cold or warm saline used (Fig. 14,*B* and *C*). With greater quantities, larger areas of the surface were subjected to thermal changes. Due to the previously mentioned complicating factors associated with heating or cooling the cavity surface, a quantitative study of these changes in the chambers of the heart could not be performed. Reciprocal polarity changes in leads from the opposite side of the ventricular wall, and even from the opposite side of the heart, were seen when larger amounts of heat or cold were applied. When the area subjected to thermal changes was small, the T-wave changes in the subendocardium and other distant areas were usually imperceptible. The magnitude of reciprocal polarity changes was always considerably less than that at the site of heat or cold application. It is unlikely that the amount of saline used caused appreciable transmission of heat or cold through the myocardium since the temperature of the saline was only a little above or below that of the dog.

The temperature change may be restricted to a very small area giving rise to local T-wave changes which can be recorded only in the limited zone of the myocardium affected by thermal changes. This was confirmed not only when a very small surface area was heated or cooled, but also when cold saline was injected intramurally, in which case T-wave changes appeared in the region of injection but not at the epicardial and endocardial surfaces. Similar conspicuous T-wave changes could be induced when electrodes 1 to 2 millimeters apart were heated or cooled. These T-wave changes were recorded only from the electrode subjected to heat or cold itself, but not from those 1 to 2 millimeters distant.

When large amounts of heat or cold were applied to the epicardial or endocardial surfaces of the heart, opposite but smaller T-polarity changes were observed in leads from the opposite side of the wall and in leads from more distant parts of the heart. If we consider the polarity changes after heating or cooling only, an increase in positivity or negativity in one region must be balanced by equal and opposite charges in other regions. The line of transition, or the electrical dipole layer, between the zone of increased positivity and that of increased negativity, or vice versa, can be assumed to be very close to the site of thermal change. This is indicated by the conspicuous polarity changes at this site and the considerably smaller changes in distant areas. Such a con-

clusion agrees with the laws of Helmholtz,[58] which state that magnitude and distance from the source of change are inversely related. Since, under physiologic conditions, the T polarity did not necessarily show a reciprocal relationship, we assume that the opposite polarity changes in distant regions after the application of heat or cold are a consequence of the thermal changes only.

The observation that small amounts of heat or cold may change the T polarity at the site of thermal changes and not at 1 to 2 millimeters distance can be explained on the basis of the same physical laws. The temperature effect restricted to a small group of cells can be recorded at the site of thermal change because repolarization is altered only locally. The restriction of electrical changes to a small area results in a corresponding decrease of distant effects due to the diminution of the source of changes. Thus, at a distance of a few millimeters, T-wave changes may not be detectable.

The main direction of repolarization through the myocardium changed very little after cold or heat application. This was shown by measurements of the time difference between T apices in simultaneously recorded leads from both sides of the ventricular wall before and after application of heat or cold. A comparison of the conspicuous T-polarity changes and the changes in the time course of repolarization through the ventricular wall showed that they paralleled each other in a very few instances. Each varied independently. This seems to be further proof that polarity changes alone do not necessarily permit conclusions about the time course of repolarization as has been done in the past.[10] Conclusions based only on polarity as a measure of direction of impulse transmission may lead to serious errors.

4. *Ischemic T-Wave Changes.*—

The electrocardiographic exploration of the heart surface after ligation of a coronary artery did not reveal a uniform pattern when the animal with the chronic infarction was in the incubator. A small area of T negativity was found at the border of the infarction in some cases; over the whole area of infarction in one case only. In three animals, in which a transmural exploration of the area of T negativity close to the infarction was performed, a negative T was found only in the outer layers of the ventricular wall. We assume that a local change in the repolarization process has occurred.

In dogs with chronic infarction, it was much more difficult to demonstrate T-wave changes characteristic of myocardial ischemia than QRS changes or S-T changes. The discrepancy between our few findings and those previously reported[29] may be due to our use of an incubator. Exposure of hearts with infarcts to room temperature may have contributed to an increase of the areas with T negativity.

Application of warm saline to the areas of T negativity induces positivity in all but one case. This response indicates that live tissue underneath the area of application was able to respond to thermal changes. These changes found over an infarcted region are regarded as proof for the existance of an infarction of the patchy type as was demonstrated previously in this laboratory.[59]

Assuming that there is not complete tissue death, it is conceivable that the remaining live tissue in the region may well be able to take part in the generation of the T wave recorded on the epicardial surface.

5. *The Influence of Primary T-Wave Changes on Secondary Ones.*—

In the five dogs in which the left bundle of His was cut, the application of warm or cold saline to the epicardial surface of the heart caused the same changes as those in similar experiments on normal hearts. The secondary T-wave changes due to bundle branch block, i.e., deep inversion, could be altered by application of heat. Analogous results were obtained when premature ventricular contractions were induced mechanically. The secondary T-wave changes of these beats were altered by heat or cold in the same way as in left bundle branch block.

SUMMARY AND CONCLUSIONS

The electrical recovery process of the heart was studied in experiments on forty-nine dogs. The animals were placed in an incubator in order to approach a physiologic situation. Surface, intramural, and cavity leads were taken by means of unipolar plunge electrodes.

Simultaneously recorded leads from the ventricular surface and the underlying subendocardium showed positive T polarity on both sides of the wall in 47.4 per cent on the left and in 70.7 per cent on the right ventricle. In nine animals intracavitary leads were taken together with subcutaneous leads from the region overlying the ventricle before the chest was opened. In all these experiments, the T waves from the right and left cavity as well as from the chest wall were found to be positive. This confirmed the results obtained in the incubator, that the T polarity from opposite sides of the ventricular wall is not necessarily reciprocal. The fact that this disagrees with previous reports may be due to the cooling effect of room temperature upon the myocardium or other unphysiologic changes in earlier investigations.

The time course of repolarization was studied in simultaneous leads from the ventricular surface and the underlying subendocardium. The T apex was used as reference point. The subendocardium preceded the epicardium by a statistically significant mean time difference strongly suggesting that repolarization takes place in most instances earlier in the subendocardial than in the epicardial region.

The electrical recovery of the right ventricular surface was found to terminate before that of the left in the majority of cases when simultaneous leads from both surfaces were compared.

There was no statistically significant difference in time between the T apices from the apex and base of each ventricle. The fact that repolarization may take place almost simultaneously on apex and base may explain in part the difference in time course between depolarization and repolarization of the myocardium, which results in the normal ventricular gradient.

The time course of repolarization showed no correlation with the polarity of the T wave. Each seemed to vary independently.

The influence of thermal changes on the repolarization process was investigated by applying warm and cold saline to the epicardial and endocardial surfaces of the heart. Cold increased the negativity, heat the positivity of the T wave. These T-wave changes are probably due to biochemical changes of undetermined nature. With an increase in the size of the area heated or cooled, the T-wave changes in this area increased concomitantly. When the area of thermal change was kept small, local T-wave changes occurred without changes in distant, subendocardial, or adjacent leads. With an increase in the area heated or cooled, reciprocal T-polarity changes could be observed in simultaneously recorded leads from the other side of the ventricular wall and from the opposite side of the heart. These changes were always smaller than those at the site of heating or cooling. The electrical alterations can be explained on the basis of the formation of a new local dipole layer as a consequence of thermal changes. Electrical changes on one side of the layer must be equal to those on the other side. The prominent changes at the site of heat or cold application are due to the proximity of the local events. The magnitude of the reciprocal polarity changes is small or imperceptible because of the distance from the source of changes.

Ischemic T-wave changes were studied after ligation of coronary arteries. In some instances, T negativity was found on the surface in a region close to the infarction. Intramural exploration of the infarcted region by plunge electrodes showed the T negativity to be restricted to the outer layers. Application of warm saline to the surface resulted in reversal of the T wave to positivity in most instances, indicating the presence of live tissue in these regions. Obviously, more experiments should be done to investigate ischemic T-wave changes before conclusions may be made.

The influence of primary T-wave changes on secondary ones was investigated in dogs with left bundle branch block and during premature ventricular contractions. Application of heat or cold on the ventricular surface induced the same T-wave changes as those produced in normally conducted beats. This seems of importance in clinical electrocardiography, especially in cases of bundle branch block complicated by myocardial infarction.

The experimental results recorded here emphasize the fact that the T wave is extremely susceptible to a wide variety of stimuli and may be altered as a result of small and minor changes in environment. Thus, clinically, T-wave changes must be carefully evaluated to avoid misinterpretation.

REFERENCES

1. Ashman, R., and Hull, E.: Essentials of Electrocardiography, New York, 1941, The Macmillan Company.
2. Ashman, R., and Hull, E.: The Chest and the Heart, Vol. II, Springfield, Ill., 1948, Charles C Thomas, Publisher.
3. Wilson, F. N., MacLeod, A. G., and Barker, P. S.: Tr. A. Am. Physicians **46**:29, 1931.
4. Wilson, F. N., MacLeod, A. G., Barker, P. S., and Johnston, F. D.: Am. Heart J. **10**:46, 1934.
5. Ashman, R., and Byer, E.: Am. Heart J. **25**:16, 1943.
6. Ashman, R., and Byer, E.: Am. Heart J. **25**:36, 1943.
7. Ashman, R., Gardberg, M., and Byer, E.: Am. Heart J. **26**:473, 1943.
8. Ashman, R.: Am. Heart J. **26**:495, 1943.

9. Grant, R. P., and Estes, E. H.: Spatial Vector Electrocardiography, Philadelphia, New York, Toronto, 1952, Blakiston Company.
10. Hellerstein, H. K., and Liebow, I. M.: Am. Heart J. **39**:35, 1950.
11. Pipberger, H., Kaelin, R., and Rossier, P. H.: Cardiologia **27**:166, 1955.
12. Bayliss, W. M., and Starling, E. H.: Month. Internat. J. Anat. Physiol. **9**:256, 1892.
13. Eppinger, H., and Rothberger, C. J.: Wien. klin. Wschnschr. **22**:1091, 1909.
14. Mines, G. R.: J. Physiol. **46**:188, 1913.
15. Smith, F. M.: Arch. Int. Med. **25**:673, 1920.
16. Wilson, F. N., and Hermann, G. R.: Heart **8**:229, 1921.
17. Smith, F. M.: Heart **10**:391, 1923.
18. Wilson, F. N., and Finch, R.: Heart **10**:275, 1923.
19. Hoff, H. E., and Nahum, L. H.: Am. J. Physiol. **131**:700, 1941.
20. Nahum, L. H., Hoff, H. E., and Kaufman, W.: Proc. Soc. Exper. Biol. & Med. **46**:395, 1941.
21. Rosenblueth, A., and Ramos Garcia, J.: Arch. Inst. Cardiol. México **15**:101, 1945.
22. Byer, E., Toth, L. A., and Ashman, R.: Am. J. Physiol. **149**:264, 1947.
23. Nims, L. F., Kartin, B., Chernoff, H. M., and Nahum, L. H.: Fed. Proc. **7**:86, 1948.
24. Akman, L. C., Silber, E. N., Miller, A. J., and Katz, L. N.: Am. J. Physiol. **159**:492, 1949.
25. Chernoff, H. M., and Nahum, L. H.: Fed. Proc. **8**:24, 1949.
26. Dowling, C. V., and Hellerstein, H. K.: Am. Heart J. **41**:58, 1951.
27. Lepeschkin, E.: Fed. Proc. **10**:81, 1951.
28. Lepeschkin, E.: Modern Electrocardiography, Vol. 1, Baltimore, 1951, The Williams & Wilkins Company.
29. Bayley, R. H., and La Due, J. S.: Am. Heart J. **28**:54, 1944.
30. Burch, G.: M. Clin. North America **29**:464, 1945.
31. Wilson, F. D., Rosenbaum, F. F., Johnston, F. D., and Barker, P. S.: Arch. Inst. Cardiol. México **14**:201, 1945.
32. Sodi-Pallares, D., Brumlik, J., Mendoza, J., and Cabrera, E.: Arch. Inst. Cardiol. México **15**:241, 1945.
33. Routier, R.: Acta Cardiol. **1**:312, 1946.
34. Meyer, P.: Brit. Heart J. **11**:137, 1949.
35. Somerville, W., and Wood, A.: Brit. Heart J. **11**:305, 1949.
36. Dressler, W., Roesler, H., and Schwager, A.: Am. Heart J. **39**:217, 1950.
37. Dressler, W., Roesler, H., and Schwager, A.: Am. Heart J. **39**:544, 1950.
38. Papp, C., and Smith, K. S.: Circulation **11**:53, 1955.
39. Lepeschkin, E., and Surawicz, B.: Am. Heart J. **46**:9, 1953.
40. Prinzmetal, M.: Unpublished observations.
41. Massumi, R. A., Goldman, A., Rakita, L., Kuramoto, K., and Prinzmetal, M.: Am. J. Med. **19**:832, 1955.
42. Groedel, F. M., and Borchardt, P. R.: Direct Electrocardiography of the Human Heart, New York, 1948, Brooklyn Medical Press, Inc.
43. Lenègre, J., and Maurice, P.: Paris méd. **35**:23, 1945.
44. Hecht, H. H.: Am. Heart J. **32**:39, 1946.
45. Sodi-Pallares, D., Vizcaíno, M., Soberón, J., and Cabrera, E.: Am. Heart J. **33**:819, 1947.
46. Battro, A., and Bidoggia, H.: Am. Heart J. **33**:604, 1947.
47. Duchosal, P. W., Ferrero, C., Doret, J. P., Andereggen, P., and Rilliet, B.: Cardiologia **13**:113, 1948.
48. Gibert-Queraltó, J., Torner-Soler, M., Paravasini-Parra, J., and Morato-Portell, J. M.: Medicina Clinica (Barcelona) **7**:299, 1949.
49. Levine, H. D., Hellems, H. K., Dexter, L., and Tucker, A. S.: Am. Heart J. **37**:64, 1949.
50. Kert, M. J., and Hoobler, S. W.: Am. Heart J. **38**:97, 1949.
51. Seligmann, A., Steinberg, M. F., Kroop, I. G., and Grishman, A.: Bull. New York Acad. Med. **25**:443, 1949.
52. Sodi-Pallares, D., Estandia, A., Soberón, J., and Rodriguez, I.: Am. Heart J. **40**:655, 1950.
53. Gibert-Queraltó, J., Torner Soler, M., Paravisini-Parra, J., and Morato-Portell, J. M.: Medicina Clinica (Barcelona) **8**:400, 1950.
54. Kossman, C. E., Berger, A. R., Rader, B., Brumlik, J., Briller, S. A., and Donnelly, J. H.: Circulation **2**:10, 1950.
55. Kossman, C. E., Berger, A. R., Briller, S. A., Rader, B., and Brumlik, J.: Circulation **1**:902, 1950.
56. Hartmann, I., Veyrat, R., Wyss, O. A. M., and Duchosal, P. W.: Cardiologia **25**:317, 1954.
57. Schaefer, H.: Das Elektrokardiogramm, Berlin-Goettingen-Heidelberg, 1951, Springer-Verlag.
58. Helmholtz, H.: Ann. d. Phys. u. Chem., Leipz. **29**:222, 1853.
59. Prinzmetal, M., Kennamer, R., and Maxwell, M.: Am. J. Med. **17**:614, 1954.

THE AXOSTAT

IV. An Analysis of the Planar and Spatial Electrocardiographic Indices of Normal Subjects as Referred to an Orthogonalized Lead System

Daniel A. Brody, M.D.

Memphis, Tenn.

IN THE preceding paper of this series we pointed out the possible merits of referring electrocardiographic data to a lead system whose axes are mutually orthogonal.[1] However, there did not appear to be any valid basis on which to devise such a lead system until the recent demonstration by Frank that the electrocardiographic equipotentials on the body surface of a normal male subject closely resembled those on an electrically homogeneous model patterned from the subject.[2] In view of this demonstration the tentative conclusion seemed warranted that electrocardiographic frames of reference determined in the case of three-dimensional models may apply with reasonable accuracy to the human body.

On this basis we computed tables of correction factors which, when applied to results derived from the equilateral tetrahedral frame of reference,[3] provide directional electrocardiographic data referred to a presumably orthogonalized lead axis system. The present study is concerned with an analysis of the results obtained by applying these correction factors to the planar and spatial electrocardiographic indices of the previously reported group of 102 normal, youthful adults.[1]

METHODS AND MATERIALS

The details of instrumentation and clinical evaluation of the subjects were described in the preceding report.[1]

The scalene tetrahedron employed as a frame of reference in this study is that which Frank determined on a three-dimensional, electrically homogeneous model of the human body.[4] The apices of the tetrahedron correspond to the electrodes, R, L, and F, of conventional extremity lead electrocardiography, and to Wilson's back electrode, B.[3] In addition, a synthetic reference point, A, was employed, which lay in image space half way between the apices R and L. This point was obtained by tying the right and left arms together through equal resistors of relatively large magnitude.

From the Cardiovascular Laboratory, Department of Medicine, University of Tennessee, Memphis.
This study was supported by research grant H-1362-C3 of the National Heart Institute, U. S. Public Health Service.

Received for publication April 7, 1956.

In this study the RLF plane of the tetrahedron was designated as the "frontal" plane, and the ABF plane as the "sagittal" plane. The line AF, which is common to both of these planes, was designated as the "vertical" axis of the reference system. These designations are not completely accurate since the RLF plane forms an angle of 11 degrees with the anatomic frontal plane, the ABF plane forms an angle of 3 degrees with the anatomic sagittal plane, and the line AF is not exactly parallel with the anatomic vertical axis.* Furthermore, the RLF and ABF planes intersect at an angle of 83 degrees rather than at right angles.

Despite these inconsistencies, the above designations were adopted in order to make the corrected data more nearly comparable with the original observations. A few representative data were calculated with respect to the RLF plane and a plane passing through the line AF at right angles to the RLF plane. This method of exact mathematical orthogonalization was abandoned because it was quite tedious and did not materially affect the results.

In the equilateral tetrahedron the RLF and ABF planes are bounded by equilateral and isosceles triangles, respectively. In the scalene tetrahedron they are bounded by scalene triangles. The principles by which data in one triangular frame of reference may be transposed to a triangular frame of different shape have been described in some detail in previous reports.[5-7] The correction tables employed here were based upon these principles.

RESULTS

Planar Electrocardiographic Indices.—The effect of orthogonalization of the axes upon the direction of mean QRS and T vectors in their frontal and sagittal projections is summarized in the illustrations and in Table I. It is

TABLE I. COMPARISON OF PLANAR ELECTROCARDIOGRAPHIC INDICES AND ANGLES BETWEEN MEAN SPATIAL VECTORS AS REFERRED TO SCALENE AND EQUILATERAL TETREHEDRAL FRAMES

ELECTROCARDIOGRAPHIC INDEX	PROJECTION	REFERENCE FRAME			
		SCALENE		EQUILATERAL	
		AVERAGE VALUE (DEGREES)	STANDARD DEVIATION (DEGREES)	AVERAGE VALUE (DEGREES)	STANDARD DEVIATION (DEGREES)
Direction of mean QRS	Frontal	35.7	±20.0	62.9	±22.4
	Sagittal	31.6	±16.4	52.1	±19.7
Direction of mean T	Frontal	24.3	±10.4	52.0	±17.1
	Sagittal	38.0	±18.4	58.6	±19.9
Mean QRS direction minus mean T direction	Frontal	11.2	±17.9	10.9	±21.0
	Sagittal	−6.3	±17.6	−6.3	±21.0
Angle between mean spatial vectors	,	21.4	±10.5	22.0	±12.1

*The direction cosines of a line normal to the RLF plane are 0.134; −0.133; and −0.982. The direction cosines of a line normal to the ABF plane are 0.999; 0.050; and 0.002. The direction cosines of the line AF are 0.049; −0.989; and 0.141.

evident from these that the frontal and sagittal projections of both the QRS and T vectors are much more nearly horizontal in the scalene (orthogonalized) frame of reference than in the equilateral frame of reference. Apparently orthogonalization affects the mean QRS and T vectors to essentially the same extent since the average value of the angular difference between the two vectors is virtually the same in the two systems of reference.

TABLE II. FREQUENCY DISTRIBUTION OF ANGLE BETWEEN MEAN SPATIAL QRS AND T VECTORS ACCORDING TO SEX AND BODILY HABITUS

ANGLE (DEGREES)	ORTHOGONALIZED AXES										TOTAL
	BODILY HABITUS										
	ASTHENIC		SLENDER		AVERAGE		ATHLETIC		OBESE		
	M	F	M	F	M	F	M	F	M	F	
5	–	–	–	1	2	2	–	1	–	1	7
10	–	–	2	–	2	4	–	–	1	1	10
15	1	–	3	3	4	7	3	–	3	–	24
20	–	–	4	4	6	6	1	–	–	2	23
25	1	–	3	3	3	2	1	–	1	–	14
30	–	–	2	1	4	3	–	–	1	–	11
35	–	–	1	3	1	1	–	–	–	–	6
40	–	–	–	2	–	–	–	–	–	1	3
45	–	–	–	1	–	–	–	–	–	–	1
50	–	–	–	–	1	–	–	–	–	–	1
55	–	–	–	1	1	–	–	–	–	–	2
Total											102

In general the dispersion of data is somewhat less in the scalene frame than in the equilateral frame. However, this reduction of scatter is only slight to moderate except for the frontal plane projections of the mean T vectors. In this case the standard deviation for the scalene system is ±10.4 degrees as compared to ±17.1 degrees for the equilateral system. The least improvement is found in the sagittal projections of the T vectors, in which case the standard

TABLE III. MEAN SPATIAL QRS AND T LOCI (REGRESSION OF SAGITTAL PLANE ANGLE ON FRONTAL PLANE ANGLE)

VECTOR	FRAME OF REFERENCE	INTERCEPT ON ORDINATE (DEGREES)	SLOPE	STANDARD DEVIATION (DEGREES)	COEFFICIENT OF CORRELATION
Mean QRS	Scalene	9.2	0.63	±10.6	0.77
	Equilateral	7.1	0.72	±10.2	0.85
Mean T	Scalene	4.4	1.39	±11.5	0.78
	Equilateral	4.8	1.03	±11.3	0.82

deviation is ±19.9 degrees for the equilateral system as compared to ±18.4 degrees for the scalene frame.

Spatial Electrocardiographic Indices.—The average value of the angle between the mean spatial QRS and T vectors is virtually identical in the two sys-

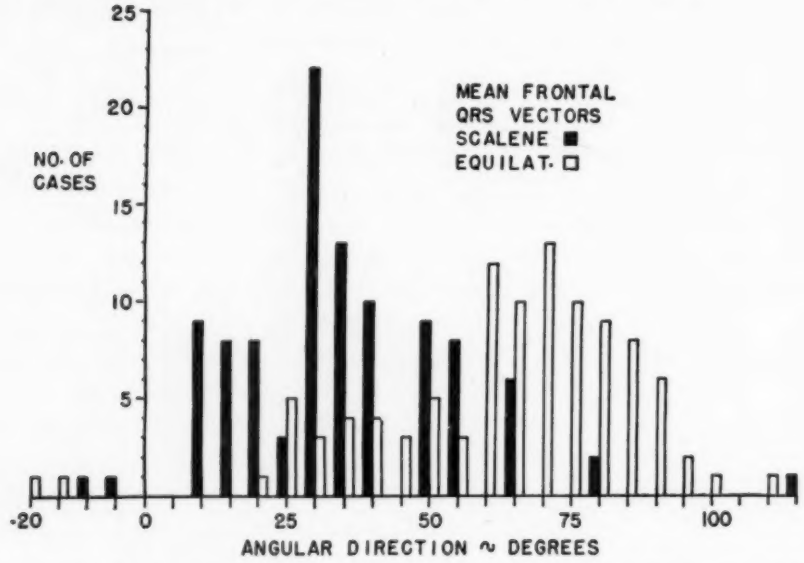


Fig. 1.—Distribution, according to angular directions, of mean frontal QRS vectors in a corrected (scalene) and an uncorrected (equilateral) frame of reference.

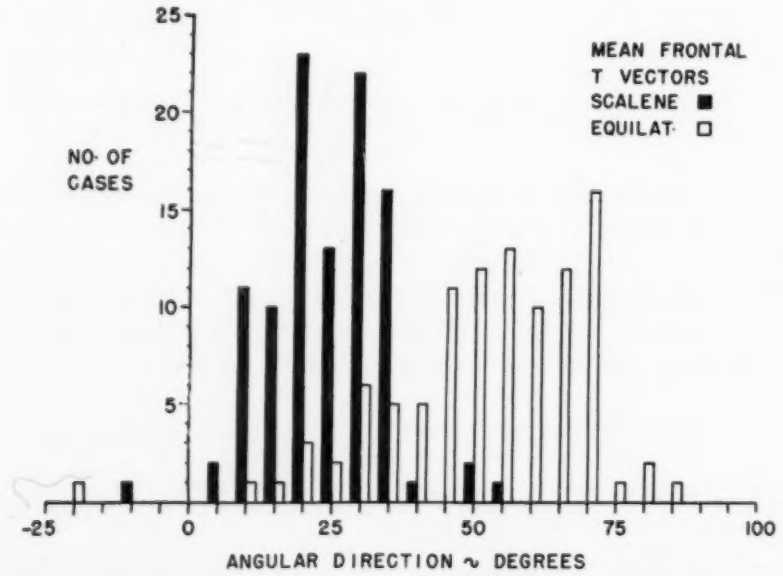


Fig. 2.—Distribution, according to angular directions, of mean frontal T vectors in a corrected (scalene) and an uncorrected (equilateral) frame of reference.

tems. The standard deviation of this angle is ±10.5 degrees in the orthogonalized system as compared to ±12.1 degrees for the uncorrected system. The total range of spatial angular values is ten degrees less in the scalene frame of reference

than in the equilateral frame. As was the case with the uncorrected spatial angles, the magnitude of the correct spatial angles appears to be independent of the sex and bodily habitus of the subjects (Table II).

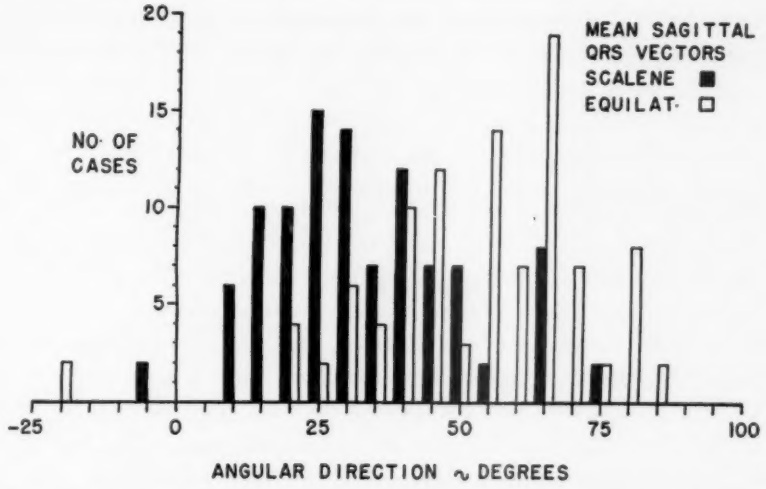


Fig. 3.—Distribution, according to angular directions, of mean sagittal QRS vectors in a corrected (scalene) and an uncorrected (equilateral) frame of reference.

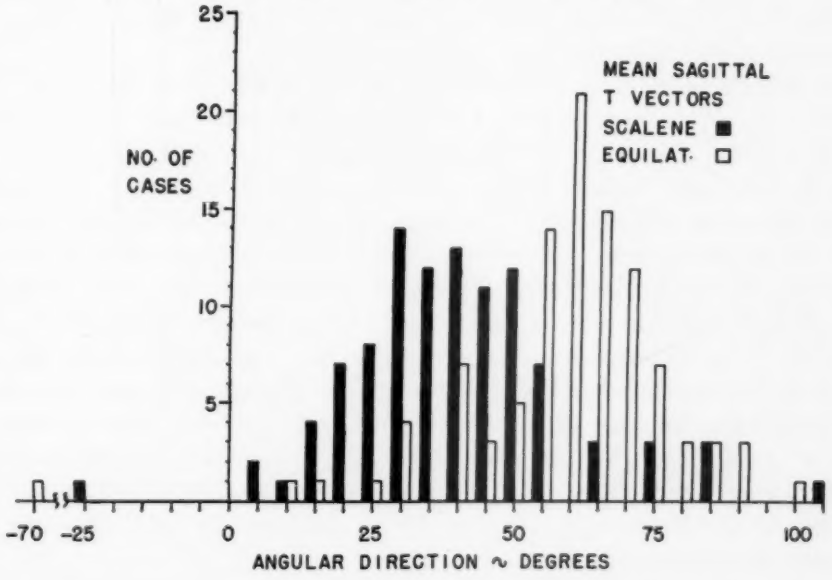


Fig. 4.—Distribution, according to angular directions, of mean sagittal T vectors in a corrected (scalene) and an uncorrected (equilateral) frame of reference.

It was demonstrated in the earlier report that the sagittal plane directions of mean QRS or T vectors bear a statistically significant relationship to the frontal plane directions of the same vectors.[1] This relationship was defined by the regression of the dependent variable (sagittal plane directions) upon the independent variable (frontal plane directions). The regressions, thus determined, indicated that mean QRS and T vectors are not randomly oriented

in space, but tend, rather, to lie along well-defined spatial curves referred to as mean spatial QRS and T loci.

The mean spatial loci determined for the scalene frame of reference are shown in Table III. It is evident from this table that these loci are somewhat less significant in the scalene frame as compared to the equilateral frame, since the standard deviations about the regression lines are slightly greater, and the correlation coefficients are somewhat smaller.

DISCUSSION

The tetrahedral frame of reference consists essentially of three electrocardiographic connections whose lead vectors[8] are linearly independent. Such an arrangement presumably provides a reliable reference system if the magnitude and orientation of the lead vectors are accurately known. In the equilateral configuration these values are not known, but assumed; whereas the scalene configuration is based on experimental observations.

Despite the theoretical advantages of the scalene system, it produced only slight to moderate reduction of planar index and mean spatial QRS-T angle variability. The equilateral configuration proved somewhat superior to the scalene frame for defining the mean QRS and T loci. This latter result, however, does not argue against the validity of the scalene system because these particular indices are simply arbitrary statistical devices for correlating frontal and sagittal plane observations.

The failure of electrocardiographic data to exhibit a striking reduction of variability in an orthogonalized axis system suggests that the variability is essentially of cardiac origin. However, there are a number of reasons for believing that a single scalene frame such as employed here does not apply with equal accuracy to all subjects, or even to all phases of the electrocardiographic cycle in the same subject: (a) The left arm connection is unreliable for accurate registration of the horizontal heart-vector component[2]; (b) The configuration of the Burger triangle varies significantly from subject to subject[9]; (c) The position of Wilson's back point as determined in a group of ninety-six subjects is rather widely scattered in image space[10]; (d) The heart cannot be represented as a single, fixed-location dipole in all subjects[11]; and (e) The position of the equivalent cardiac dipole, as studied by the cancellation technique, may be different during repolarization as compared to depolarization.[12,13] Undoubtedly, errors due to the last two factors would be considerably minimized by the use of suitably compounded lead connections.[14,15]

Despite these numerous defects, a single scalene tetrahedron is probably superior to the equilateral tetrahedron as a frame of reference. From the practical point of view, however, the scalene tetrahedron apparently does not possess sufficient merit to warrant its routine application to the analysis of mean spatial QRS and T vector orientation.

SUMMARY

1. The planar electrocardiographic indices (angular directions of mean frontal and sagittal QRS and T vectors) and spatial indices (angle between

mean spatial QRS and T vectors, mean spatial QRS and T vector loci) of 102 normal, youthful adults were determined with respect to a corrected frame of reference. These results were compared with similar determinations made on the same subjects with respect to an uncorrected frame of reference.

2. All of the planar indices, and the mean spatial QRS-T angles exhibited some reduction of scatter, ranging from slight to moderate, within the corrected frame of reference.

3. The mean spatial QRS and T vector loci exhibited slightly less scatter and better coefficients of correlation within the uncorrected frame of reference.

4. The corrected frame of reference does not appear to possess sufficient merit to warrant its routine application to the analysis of mean QRS- and T-vector orientation.

REFERENCES

1. Brody, D. A.: Am. Heart J. **50**:610, 1955.
2. Frank, E.: Circulation Research **3**:243, 1955.
3. Wilson, F. N., Johnston, F. D., and Kossman, C. E.: Am. Heart J. **33**:594, 1947.
4. Frank, E.: Circulation **10**:101, 1954.
5. Brody, D. A., and Romans, W. E.: Am. Heart J. **45**:253, 1953.
6. Brody, D. A.: Am. Heart J. **48**:730, 1954.
7. Little, R. C., Brody, D. A., and Tacket, H. S.: Am. Heart J. **48**:721, 1954.
8. Burger, H. C., and van Milaan, J. B.: Brit. Heart J. **8**:157: 1946; **9**:154, 1947; **10**:229, 1948.
9. Brody, D. A., Erb, B. D., and Romans, W. E.: Am. Heart J. **51**:211, 1956.
10. Burger, H. C., van Milaan, J. B., and Klip, W.: Am. Heart J. **51**:26, 1956.
11. Nelson, C. V., and Hecht, H. H.: Fed. Proc. **14**:107, 1955.
12. Frank, E.: Circulation **11**:937, 1955.
13. Brody, D. A.: Unpublished observations.
14. Brody, D. A., and Romans, W. E.: J. Appl. Physiol. **6**:745, 1954.
15. Schmitt, O. H., and Simonson, E.: Arch. Int. Med. **96**:574, 1955.

STUDIES ON THE ANTICOAGULANT PHENINDIONE

II. Details Regarding Its Administration in Two Hundred Cases

Herbert S. Sise, M.D., William C. Moloney, M.D., and
Charles G. Guttas, M.D.

Boston, Mass.

THE use of phenindione (P.I.D.) clinically as an anticoagulant has stemmed from the original findings in animals that indanediones possessed prothrombopenic properties.[1,2] Clinical reports[3-8] suggest a superiority over bishydroxycoumarin since control is said to be achieved with greater facility as a result of quicker and more transient effect. The finding that Vitamin K_1 Emulsion rapidly reverses the effects of phenindione on the coagulation mechanism enhances its potential usefulness.[9] The present report based on the routine use in two hundred hospitalized patients confirms the impression that this preparation when properly administered may be used safely and with facility. The properties of P.I.D. in relation to its clinical use are also described.

MATERIALS AND METHODS

Two hundred consecutive unselected hospitalized cases to whom phenindione was given were reviewed. Treatment was initiated and maintained by the resident and intern staff of the Medical and Surgical Services of the Boston City Hospital. The management was based on an information sheet supplied to the personnel and which outlined dosage, contraindications, and suggestions in regard to routine observation. The dose recommended after initial trial of various schedules was set at 200 mg. followed by 100 mg. in twelve hours. After this priming dose, the daily dose was adjusted to the prothrombin time so that the latter was kept between 26 and 36 seconds. A history inquiring particularly into bleeding tendencies, renal or liver impairment, and gastrointestinal lesions was asked for, as well as a control prothrombin time, NPN, stool, and urine. In compelling circumstances the drug was given without these control laboratory procedures and consequently sometimes in the presence of what had heretofore been considered contraindications. Daily prothrombin times and biweekly stools and urines were requested during treatment.

The diagnosis of phlebitis, pulmonary embolus, congestive failure, peripheral vascular disease, and acute coronary insufficiency was based on the usual clinical criteria. Since under the best of circumstances no completely definitive diagnosis

From Tufts Medical Services and Anticoagulant Laboratory, Boston City Hospital, and the Department of Medicine, Tufts University School of Medicine.

Supported by a grant from the National Heart Institute (H-1058).
Received for publication April 4, 1956.

can be made without post-mortem study or surgery, the diagnosis in most of the cases possessed an unknown degree of probability. The diagnosis of myocardial infarct was made only with unequivocal acute changes by electrocardiogram with characteristic serial changes showing the evolution of the process. For the purpose of further elucidating the distribution of cases of myocardial infarction of various severity, they were graded 1 to 4 on the following point score basis:

Shock lasting over twelve hours	2 points
Prolonged, repeated or recurrent substernal pain	2 points
Temperature 101° or over	1 point
White blood count 15,000 or over	1 point
Pulmonary edema	1 point
Congestive failure	1 point
Significant arrhythmia	1 point
History of previous myocardial infarct	1 point
	Point Score
Group I	0
Group II	1–2
Group III	3–5
Group IV	6 or more

Excessive P.I.D. effect was considered to be present when the prothrombin time exceeded 60 seconds.

Bleeding was divided into three grades: Grade 1, minor bleeding phenomena such as microscopic hematuria for which P.I.D. was not stopped; Grade 2, bleeding for which P.I.D. was stopped; Grade 3, fatal bleeding episode. Prothrombin determinations were done by Quick's one-stage procedure,[10] using commercial dried rabbit brain thromboplastin (Difco) and 0.01M calcium chloride. Normal control subjects showed prothrombin times of 12 to 14 seconds. By dilution

TABLE I. GENERAL SUMMARY OF 200 PATIENTS GIVEN PHENINDIONE

CLINICAL DIAGNOSIS	NO. OF CASES	THROMBO-EMBOLIC COMPLICATIONS (NO. OF CASES)	DEATHS	GRADE OF BLEEDING			EXCESSIVELY LONG PROTHROMBIN TIME
				1	2	3	
Phlebitis	31	2 (6.4%)	1 (3%)	1	6	0	3
Pulmonary embolus	26	3 (11.6%)	4 (15.4%)	1	1	0	2
Peripheral vascular disease	15	2 (13.3%)	5 (20.0%)	0	1	1	2
Myocardial infarcts							
Group I	35	0 (0%)	0 (0%)	0	0	0	0
Group II	26	1 (3.8%)	0 (0%)	0	0	0	3
Group III	16	1 (6.3%)	3 (18.7%)	1	0	0	0
Group IV	16	4 (25%)	7 (43.8%)	1	4	0	5
Other (coronary insufficiency, congestive failure, etc.)	35	1 (2.8%)	2 (5.7%)	3	1	0	3
Totals	200	14 (7%)	22 (11%)	7 (3.5%)	13 (6.5%)	1 (0.5%)	20 (10%)

curves with fresh normal plasma adsorbed with $BaSO_4$ (25 mg. per milliliter) the prothrombic activity at 26 seconds represented 10 per cent, and at 36 seconds 5 per cent. Specific determination of prothrombin by the two-stage method of Ware and Seegers[11] in selected cases where comparisons were valid[12] indicated that the prothrombin levels actually were near this range. Proconvertin determinations by the method of Owren[13] indicated levels of 3 to 15 per cent when prothrombin times were between 26 and 36 seconds.

RESULTS

Dosage.—A priming dose of 200 mg. of P.I.D. initially and 100 mg. in 12 hours was used in 142 patients. A satisfactory response was considered to be a prothrombin time of 20 to 36 seconds 24 to 36 hours later and was achieved in

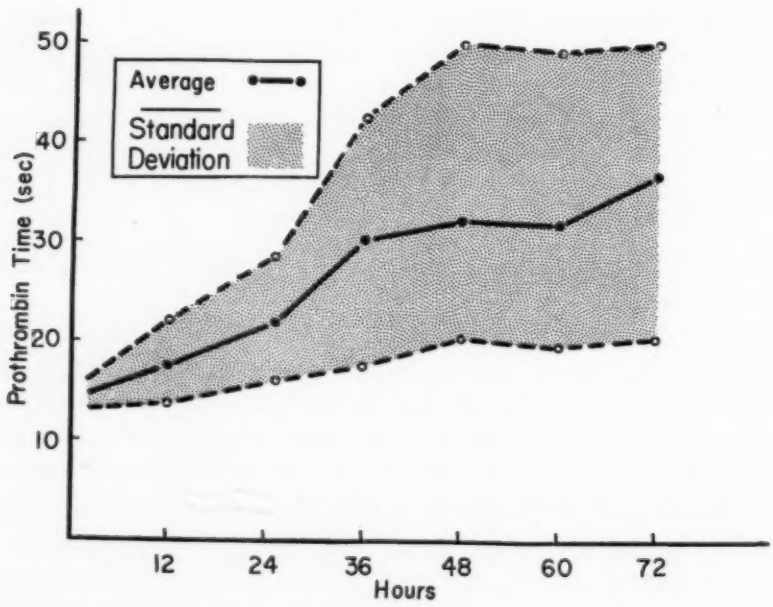


Fig. 1.—Response of prothrombin time to phenindione showing average values and deviation from the average. The effect is apparent at twelve hours and becomes fully manifest by thirty-six hours.

106 patients (74.5 per cent). This dose resulted in initially low prothrombin times in 24 patients (16.9 per cent) and excessive prothrombin times in twelve patients (8.5 per cent). Other dosage schedules were used, and eighteen of thirty patients (60 per cent) showed a satisfactory result where a 12-hour schedule was used; nine patients (30 per cent) showed insufficient response; and three patients (10 per cent) showed excessive response. When single doses in 24 hours were used in eighteen patients, only four (22 per cent) showed a satisfactory response, twelve (67 per cent) insufficient and two (11 per cent) excessive responses. There were no cases where there was no response. It appeared that a 12-hour dosage schedule was necessary for a satisfactory response. Since the average patient required the larger dosage, it is recommended that the initial dose be 200 mg. followed by 100 mg. in 12 hours rather than 100 mg. every 12

hours as previously recommended by Blaustein. In elderly, ill, debilitated, or other patients, or where caution is indicated, the smaller dose of 100 mg. initially and 100 mg. in 12 hours is recommended. The appearance of therapeutic levels in 24 to 36 hours confirms previous observations of others (Fig 1).

Maintenance Dosage.—In 172 patients, where data were sufficient for interpretation, the daily dose of P.I.D. was averaged for the whole period of administration except the initial twenty-four- to thirty-six-hour dosage. The distribution of average daily dose is indicated in Fig. 2 and ranged from 29 to 400 mg. per day, averaging 126 mg. per day. It is apparent that there is a wide range of susceptibility to P.I.D. in the same way as there is to bishydroxycoumarin. No cases of complete resistance were encountered such as reported by Blaustein. There was no correlation of dose to sex, body weight, or age except that certain older individuals were particularly sensitive. There was more satisfactory control when the daily dose was divided into twelve-hour intervals

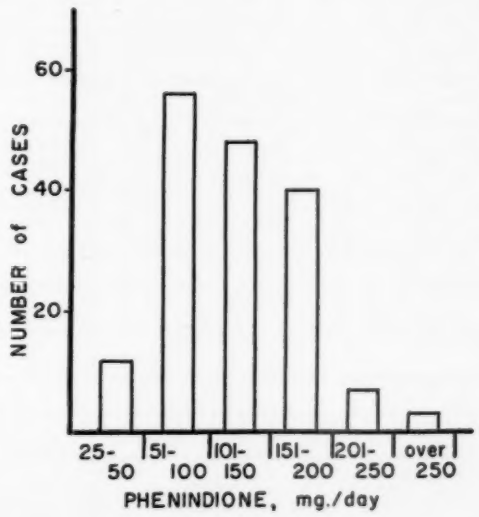


Fig. 2.—Distribution of average daily dose of phenindione used to maintain prothrombin time between twenty-six and thirty-six seconds in 172 patients.

as recommended by Jaques.[5] The dose required was 44 per cent larger in four individuals where there were sufficient data to compare single against split dosage (Fig. 3). When comparison was made on patients who had been receiving P.I.D. for over thirty days, however, it made no difference whether there was a single or split daily dose.[14] Also, those taking less than 50 mg. per day needed only one dose daily. An advantage of a twelve-hour dosage schedule is that only half the daily dose may have been given when bleeding or excess prothrombin effect is discovered, allowing earlier adjustment of dosage or discontinuance.

A cumulative effect resulting in consecutively increasing prothrombin times on the same dosage was noted in nine cases (4.5 per cent). This was noted in both sensitive and resistant individuals. There appeared to be a carry-over from day to day in other cases, but the dosage was too irregular in these instances for this to be demonstrated conclusively.

The following procedure in general is recommended as giving the most consistent results: initial dose 200 mg. and 100 mg. in twelve hours, maintenance dose 75 mg. every twelve hours until sufficient prothrombin times are at hand to indicate average, sensitive, or resistant response which may require two to four days. No trouble has been experienced when a standing order has been given for continuation of dosage automatically until changed. Final adjustment of dosage can later be achieved by averaging the daily dose over the first five to

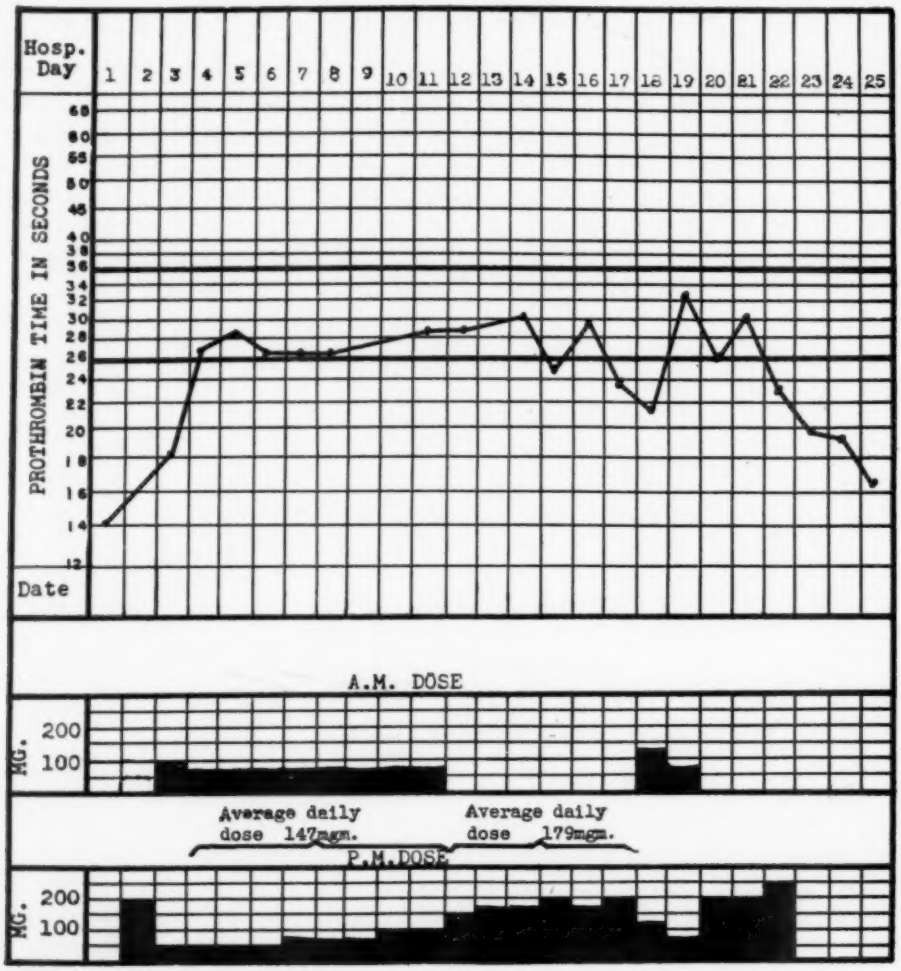


Fig. 3.—Comparison of split and single daily dose. From hospital day 2 through 11, the average daily dose was 147 mg. and the control was even. From day 12 through 17 the average daily dose was 179 mg. and the response was erratic. Following split daily doses on days 18 and 19 the prothrombin time returned to the set limits, but after resuming a single daily dose the prothrombin time again fell below therapeutic limits.

seven days, and splitting this into a twelve-hour dosage schedule. This procedure has the advantage of avoiding skipped doses which lead to erratic control. An even twelve-hour dosage is desirable.

Dissipation of Effect.—Dissipation of effect of P.I.D. was followed in forty-four cases. The majority (58 per cent) reached normal values at 36 to 72 hours after stopping treatment, but eleven (35 per cent) showed prolonged prothrombin

times 72 hours after stopping, and three (6.8 per cent), 120 hours after stopping. This is a longer period of recovery than has been reported by others and may be a reflection of the many gravely ill patients experienced in this series. It obviously indicates that some cumulative effect of at least this duration may be expected. Consequently, at least six days' observation is felt to be required before one can consider the dosage stabilized.

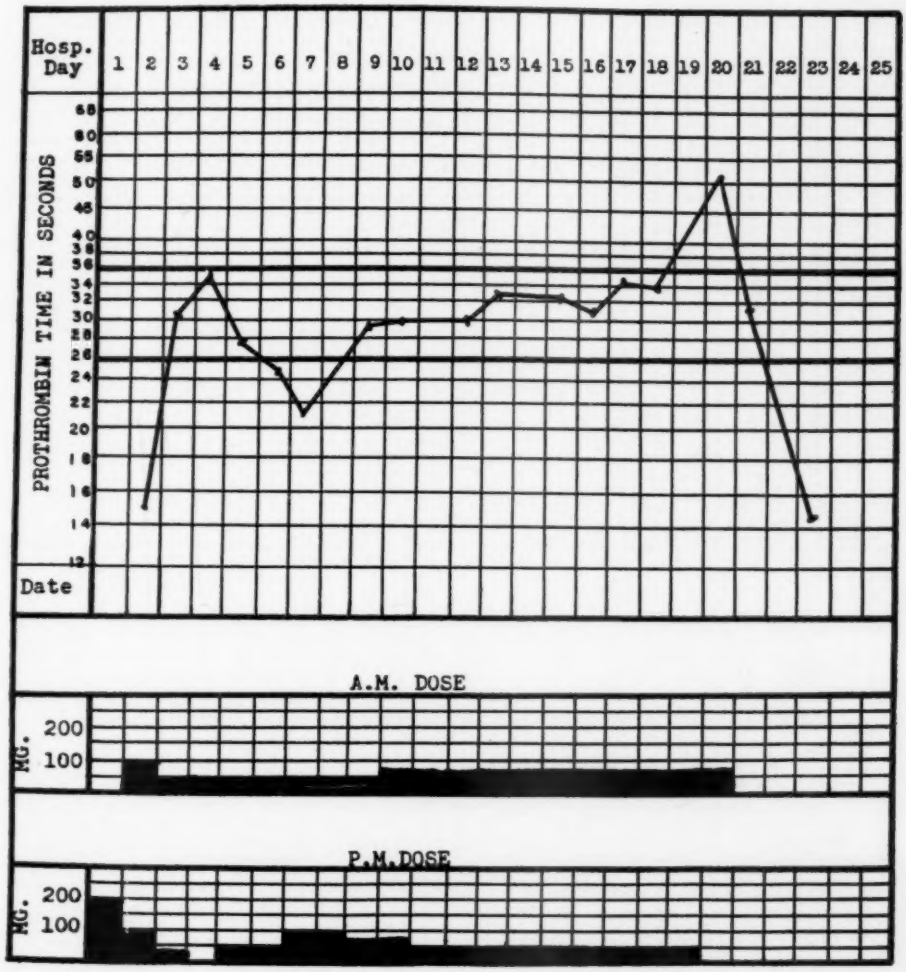


Fig. 4.—A case illustrating a cumulative effect.

Adequacy of Control.—The degree of ability to maintain prothrombin times in an anticoagulant range was calculated for each case by the percentage of days in which the prothrombin times were over twenty-four seconds. The latter figure was selected on the basis of studies on the effect of P.I.D. on the clotting mechanism, and appears at this time to represent in this laboratory approximately the lower limit at which an anticoagulant effect is noticed. A disappointingly low score was obtained (Table II). However, when one considers that the intern and resident staffs who used the preparation were not only untrained and busy, but were also constantly rotating through the wards, a clear example of

the results in general use can be estimated. A greater degree of control was noted in this series of cases than in a previously studied group with bishydroxycoumarin.[15] The most common reason for poor control appeared to be inadvertant omission of a dose.

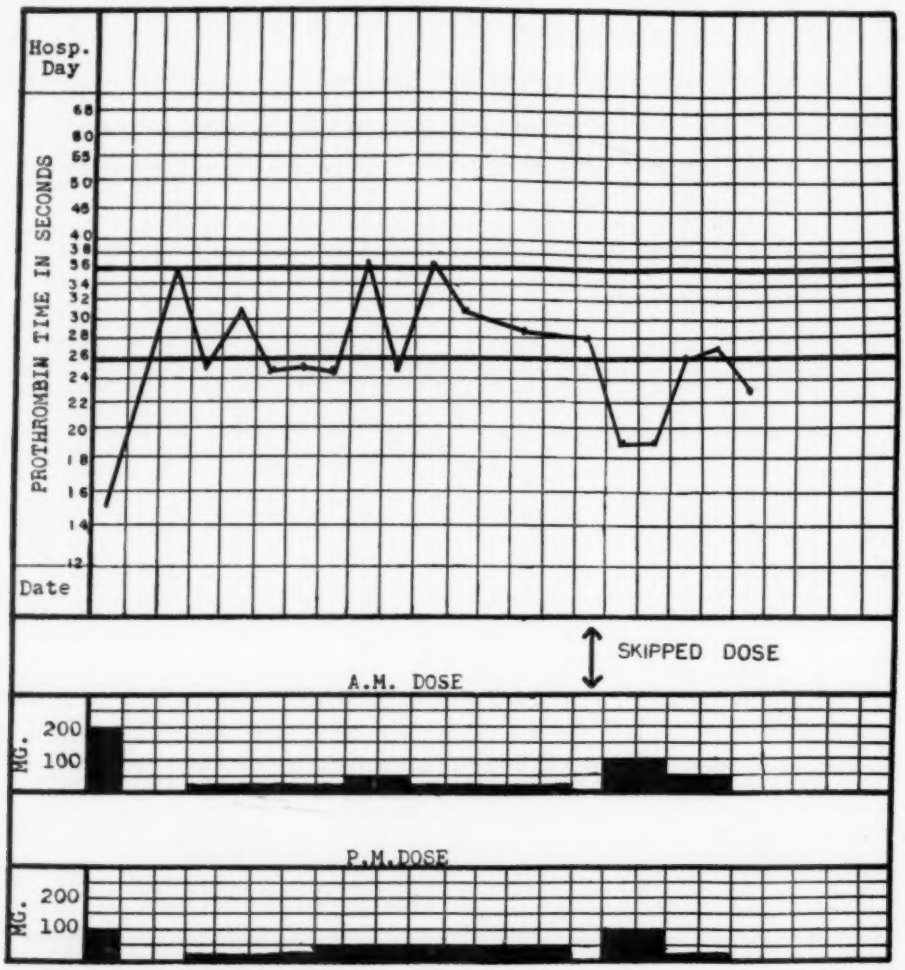


Fig. 5.—A case illustrating the effect of skipping a dose.

Excessively Prolonged Prothrombin Times.—A prothrombin time of over 60 seconds was considered to be the criterion of excessive P.I.D. effect. This occurred in twenty-one individuals (10.5 per cent) in seven of whom bleeding occurred, which was no more than microscopic hematuria, ecchymosis, or positive guaiac test on the stool. No severe hemorrhagic phenomenon was experienced in these cases. Vitamin K_1 Emulsion was used intravenously in six and orally in one. In fourteen instances, omission of the drug permanently or until therapeutic ranges were reached was all that was necessary. Vitamin K_1 Emulsion resulted in prompt return of prothrombin times below 20 seconds within three to four hours in all cases except in one individual who was moribund as result of a myocardial infarct with severe shock.

TABLE II. PERCENTAGE OF DAYS DURING TREATMENT WHEN THE PROTHROMBIN TIME WAS OVER TWENTY-FOUR SECONDS—CALCULATED FOR EACH CASE

	LESS THAN 50%	50–75%	MORE THAN 75%	TOTAL
Number of cases	55	44	99	198
Per cent of cases	27.8%	22.2%	50%	100%

Bleeding.—Evidences of bleeding occurred in twenty-one cases (10 per cent) (Table I). The degree of bleeding and relation to excessively long prothrombin time is shown in Table III. The findings suggest that microscopic hematuria may result from prolonged prothrombin time, while gastrointestinal hemorrhage occurred more frequently with prothrombin times not excessively prolonged. Of ten patients with melena, five had underlying gastrointestinal conditions, namely, duodenal ulcer, enteritis, Wangensteen drainage, recent gastrectomy, and positive guaiac stool prior to treatment, consecutively. The importance of routine stools and urines is indicated. One fatal hemorrhagic episode is herewith summarized.

TABLE III. BLEEDING EPISODES

	GRADE			TOTAL
	1	2	3	
Melena	3 (1)*	6 (1)	1	10 (2)
Hematuria	4 (2)	5 (4)		9 (6)
Ecchymosis	1 (1)	1 (1)		2 (2)
Epistaxis		1		1
Hemorrhagic cerebral infarct†		2		2
Hemothorax‡		1		1

*Figures in parentheses are cases with prothrombin times of 60 seconds or more.

†One patient with embolic hemiplegia, increasing R.B.C. in spinal fluid, and one with hemorrhagic infarct at post-mortem examination.

‡Fractured ribs and hemothorax present preceding treatment with P.I.D. for phlebitis.

A 52-year-old diabetic Negro woman with gangrene of the left leg was admitted to the surgical service. Amputation of the toes of the left foot was done and a transmetatarsal amputation was contemplated. She was placed on P.I.D. prophylactically, and prothrombin times ranged between 20 and 35 seconds. On the eighth hospital day she had epigastric pain, nausea, and vomiting. During the next three days she had tarry stools, nausea, epigastric pain, and vomiting of coffee-ground material intermittently, but attention of the house staff was not called until she began to be dyspneic. At this point she was found to be in shock with a hematocrit of 13 and a positive guaiac test on the stools. The prothrombin time had risen to 43 seconds. She was given Vitamin K_1 Emulsion, 370 mg. intravenously, slowly, and 500 c.c. of blood. Five hours later she developed pulmonary edema and an electrocardiogram showed an early septal infarct. The prothrombin time fell to 19.3 seconds, the hematocrit rose to 29, but the patient declined and died twenty-four hours later of shock and pulmonary edema.

It is quite apparent that any reasonable observation of the patient might have avoided the fatal outcome in this case.

All bleeding was slow and readily responded to Vitamin K_1 Emulsion in the six cases where administration was thought to be necessary. Analysis of bleeding in relation to the severity of myocardial infarction (Table I) gives some indication of the relative risk of administration of this anticoagulant to mildly ill versus severely ill patients. It is of interest that no bleeding was experienced in sixty-one patients with infarcts of mild severity. On the contrary, six out of thirty-two patients who were severely ill experienced bleeding. The same trend was noted in regard to the production of excessively prolonged prothrombin times in these cases.

TABLE IV. INCIDENCE OF EXCESSIVELY LONG PROTHROMBIN TIMES AND BLEEDING IN THE PRESENCE OF CERTAIN CONDITIONS

	NUMBER OF CASES	EXCESSIVE PROTHROMBIN TIMES	BLEEDING
A. *General Conditions*			
Renal disease with elevated blood urea nitrogen	13	5	4
Shock	22	7	8
Liver disease	4	1	1
Age over 70	50	10	9
Diabetes	10	1	2
Severe congestive failure	12	4	2
B. *Local Conditions*			
Duodenal ulcer	6		1
Catheter or Wangensteen	4		3
Hemothorax	2		1*
Cerebral infarct	7		2
Pleural effusion	10		0
Postoperative gastrectomy	1		1
Pre-existing rectal bleeding	2		1
Positive guaiac stools	2		1
Persistent hemoptysis	1		0
Pericardial friction rub	2		0

*Increase in degree of hemothorax.

Precautionary Conditions.—The list in Table IV indicates conditions which are considered to be contraindications to the use of anticoagulants of this type, or in the presence of which caution should be used. In many instances the indications for anticoagulation were considered to be so strong that this procedure was instituted in spite of the presence of contraindications. In others, the presence seemed to have been overlooked. In the total series, bleeding occurred in four of those without the presence of these conditions (3.6 per cent), and in eighteen of those with the presence of these conditions (20 per cent). Excessively prolonged prothrombin times occurred in approximately the same ratio. It is apparent that the presence of these factors can be expected to increase the difficulties and risks of use of anticoagulants; but unfortunately, as is implied by the preponderance in this series, the subjects most likely to require anticoagulants can be expected to have these conditions present. The fact that P.I.D. can be given under these circumstances without excessive risk is reassuring.

TABLE V. THROMBOEMBOLIC COMPLICATIONS

CASE	ORIGINAL DIAGNOSIS	THROMBOEMBOLIC COMPLICATION	DAY OF TREATMENT (P.I.D.)†	BASIS OF DIAGNOSIS
1	Phlebitis	Pulmonary embolus	2	Collapse, pleural pain, ECG changes, x-ray
2	Phlebitis	Thrombosis, inferior vena cava	2	Autopsy
3	Pulmonary embolus	?Pulmonary embolus	3	Expired suddenly; no autopsy
4	Pulmonary embolus	?Pulmonary embolus	5	Transient episode dyspnea, sweating, pulse 100; blood pressure 65/45
5	Pulmonary embolus	Healing infarct lung	2	Autopsy
6	Peripheral vascular disease	Embolus to right leg*	2	Pain, pallor, coldness of right leg
		Embolus to left middle cerebral artery*	11	Right hemiparesis
		Embolus to right leg*	30	Pain, cyanosis; right leg
7	Peripheral vascular disease	Myocardial infarct	13	Electrocardiogram
8	Myocardial infarct (Group II)	Cerebral vascular accident	3	Sudden aphasia without loss of consciousness
9	Myocardial infarct (Group III)	?Phlebitis	7	Tenderness of calf and positive Homan's sign—no redness
10	Myocardial infarct (Group IV)	Renal infarcts "recent"	13	Autopsy
11	Myocardial infarct (Group IV)	Infarct of ileum, mural thrombus, mesenteric artery thrombosis	22	Autopsy
12	Myocardial infarct (Group IV)	?Pulmonary embolus	11	Recurrent dyspnea; hemoptysis and shock; x-ray showed pulmonary edema
13	Myocardial infarct (Group IV)	??Pulmonary embolus	14	Dyspnea in paroxysms; x-ray showed pulmonary edema
14	Congestive failure	Aortic mural thrombus	19	Autopsy

*Same case with clear-cut embolic episodes occurring with adequate treatment.

†The day of treatment represents day in relation to onset of treatment that the condition was discovered. If discovered at autopsy it represents day of death. Thus it is probable that the conditions in Cases 2 and 5 occurred prior to treatment while those in 10, 11, and 14 could not be dated.

The most important conditions leading to excessive prothrombin times and bleeding are renal disease and shock.

The question has been raised as to whether a cerebral infarct resulting from an embolus can be converted into a hemorrhagic infarct[16] by anticoagulants. There can be no answer to this in the current small series. However, in one instance, a patient with a clinical cerebral embolus and initial spinal fluid showing some red cells experienced increasing stiff neck during P.I.D. therapy and increased numbers of red cells in the spinal fluid were found. The drug was stopped and the patient recovered. Another individual who had a cerebral embolus was given P.I.D.; two days later gastrointestinal bleeding was observed. The prothrombin time was not excessively prolonged and there was no stiff neck. The prothrombin time returned to normal promptly after Vitamin K_1 Emulsion intravenously, but the patient died four days later and showed a hemorrhagic infarct at post mortem. The infarction and not hemorrhage was considered by the pathologist to be the cause of death, but both cases have been considered as having had bleeding episodes resulting from P.I.D.

Thromboembolic Conditions While on P.I.D.—Since the purpose of this paper is primarily to outline the properties of P.I.D. in clinical use, the thromboembolic phenomena will be discussed elsewhere in more detail. In Table V there is listed, in condensed form, the conditions encountered. Excluding those thought to have occurred prior to treatment, twelve probable episodes occurred in ten patients while on the anticoagulant. Eight of these (75 per cent) occurred during the first 10 days, which is a period when one finds the anticoagulant effect of P.I.D. to be weak.[17]

Toxic Reactions.—Bleeding was the only toxic effect encountered in these cases. One individual not in this series, however, developed a temperature of 100 to 101°F. while receiving a second course of phenindione. This was reproduced later by feeding 50 mg. of phenindione and is similar to that case reported by Makous and Vander Veer.[18]

DISCUSSION

The search for a satisfactory anticoagulant has proceeded for over one and one-half decades, and was originally stimulated by the clinical use of heparin and bishydroxycoumarin; later, several related coumarin derivatives, e.g. Tromexan, warfarin, and Coumopyran were added to the list of materials available for clinical use. The objectives raised to the cost and necessity of parenteral administration of heparin are matched, in the case of bishydroxycoumarin, by the slowness, cumulative effect, and long period of action which have resulted in fatal hemorrhagic episodes. The present study deals entirely with details of the clinical use of P.I.D., and indicates some superiority over Dicumarol only as a result of the more rapid onset and dissipation of its effect; but bleeding and cumulative effect can be shown to be present and must be expected as a calculated risk. In subjects under, 70 years of age, without renal, hepatic, or hematologic complications, without local conditions favoring bleeding (e.g., gastrointestinal ulceration, indwelling catheter, etc.) and not severely ill or depleted, a very low incidence of bleeding can be expected. In more severely ill, over-age patients

with shock, debilitation, hepatic, renal, or gastrointestinal diseases, a fairly high incidence of hemorrhage can be expected. But if the subjects are followed carefully, P.I.D. can be administered with reasonable safety in the presence of many conditions which would contraindicate the use of Dicumarol. Although bleeding can be expected, it has been the slow variety and never a serious emergency per se. Omission of the drug, decrease in dosage, or even Vitamin K_1 Emulsion intravenously are adequate to cope with the situation. The importance of routine stools and urines is re-emphasized in this regard.

SUMMARY AND CONCLUSIONS

1. Phenindione was used routinely as an anticoagulant in 200 cases where anticoagulants were considered to be indicated. The prothrombin activity was maintained between 5 per cent and 10 per cent of normal with greater facility than in another series where bishydroxycoumarin was used.

2. In the average case the initial dose of 200 mg. followed by 100 mg. in twelve hours was the most satisfactory. In those where caution is indicated, 100 mg. followed by 100 mg. in twelve hours is recommended.

3. For predictable effects the maintenance dosage must be given every twelve hours. It ranged from 29 to 400 mg. per twenty-four hours, the mean dose being 126 mg. per day. Changes in dosage requirement were seen, as was a cumulative effect. No cases were completely insensitive.

4. The dissipation of effect usually occurred within seventy-two hours and oftentimes thirty-six hours. In a few instances up to 120 hours were required before return of prothrombin time to normal.

5. Stabilization of dosage does not occur for six days or more.

6. Bleeding occurred in twenty-one cases (10.5 per cent) with one fatality as a result of neglect (0.5 per cent). Bleeding bore less relation to prothrombin time than to severity of the patient's illness and local conditions which facilitated bleeding. Hematuria was the most common type of bleeding associated with an excessively prolonged prothrombin time. Emphasis is laid on the incidence of gastrointestinal bleeding without excess prolongation of prothrombin time. All bleeding was slow and readily responded to Vitamin K_1 Emulsion whenever required. Attention is called to the importance of routine stools and urines.

7. The relative safety of phenindione and the effectiveness of Vitamin K_1 as an antidote appear to allow a wider scope of use in critically ill patients if reasonably careful supervision is employed.

8. Sixteen episodes which were considered to be thromboembolic occurred in fourteen patients. In twelve where the episode could be dated, eight (75 per cent) occurred during the first ten days of treatment.

REFERENCES

1. Kabat, H., Stohlman, E. F., and Smith, M. I.: J. Pharmacol. & Exper. Therap. **80**:160, 1944.
2. Meunier, P., Mentzer, C., and Molho, D.: Compt. Rend. Acad. Sc. **226**:1666, 1947.
3. Soulier, J. P., and Gueguen, J.: Compt. Rend. Soc. de Biol. **141**:1007, 1947.
4. Blaustein, A. U., Croce, J. J., Alberian, M., and Richey, N.: Circulation **1**:1195, 1950.
5. Jaques, L. B., Gordon, E., and Lepp, E.: Canad. M. A. J. **62**:465, 1950.

6. Bjerklund, C. J.: Scandinav. J. Clin. & Lab. Invest. **2**:83, 1950.
7. Preston, F. W., O'Connor, W. R., Thompson, C. E., and Christensen, E. N.: Circulation **6**:515, 1952.
8. Coon, W. W., Duff, I. F., Hodgson, P. E., and Dennis, E. W.: Ann. Surg. **138**:467, 1953.
9. Guttas, C. H., Moloney, W. C., and Sise, H. S.: Blood **8**:276, 1953.
10. Quick, A. J.: The Hemorrhagic Diseases and the Physiology of Hemostasis, Springfield, 1942, Charles C Thomas, Publisher.
11. Ware, A. G., and Seegers, W. H.: Am. J. Clin. Path. **19**:471, 1949.
12. Owen, C. A., and Bollman, J. L.: Proc. Soc. Exper. Biol. & Med. **67**:231, 1948.
13. Owren, P. A., and Aas, K.: Scandinav. J. Clin. & Lab. Invest. **3**:201, 1951.
14. Drinan, F., Adamis, D., Sise, H. S., and Moloney, W. C.: Studies on the Anticoagulant Phenindione. III. Its Use in Ambulatory Patients, Am. Heart J. To be published.
15. Bresnick, E., Selverstone, L.A., Rapoport, B., Cheskey, K., Hultgren, H. N., and Sise, H. S.: New England J. Med. **243**:806, 1950.
16. Adams, R. D., and Cohen, M. E.: Bull. New England Center **9**:180, 222, 261, 1947.
17. Sise, H. S.: Proc. New England Cardiovasc. Soc. **13**:11, 1954.
18. Makous, N., and Vander Veer, J. B.: J.A.M.A. **155**:739, 1954.

Clinical Reports

PLEUROPERICARDIAL EFFUSION FOLLOWING MYOCARDIAL INFARCTION

WILLIAM MANDEL, M.D.,* AND E. C. JOHNSON, M.D.**

DENVER, COLO.

THE occurrence of bilateral pleural effusion with pericardial effusion was observed seven weeks after an acute myocardial infarction. The findings were similar to those of the postcommissurotomy syndrome. This case is being reported because of its interest and its rarity as a complication of or in association with myocardial infarction.

CASE REPORT

I. R., a 41-year-old white man, was admitted to the hospital because of sudden onset of tight, squeezing, substernal chest pain of eight hours' duration. This pain radiated to both shoulders and down the left upper extremity. His past health had been excellent, and he had no history of cardiovascular, respiratory, or allergic disease. Physical examination revealed an apprehensive, pale white man complaining of precordial pain. The blood pressure was 105/85 mm. Hg, pulse 112 per minute, and respiratory rate 24 per minute. The remainder of the physical examination was normal. The white blood and differential count, the urinalysis, the hematocrit, and the erythrocyte sedimentation rate were normal. An electrocardiogram showed changes consistent with the diagnosis of an acute anterior myocardial infarction. Later that day, the white blood count was 12,600 cells per cubic millimeter, and the erythrocyte sedimentation rate was 23 mm. per hour.

The patient was placed in an oxygen tent and anticoagulants were started. A low-grade temperature elevation was present during the first week of hospitalization. On the second hospital day, he developed pleuritic anterior chest pain that was associated with a cough productive of small amounts of nonbloody, frothy sputum. This persisted for three days. A portable chest roentgenogram on the third hospital day showed a right-sided pleural effusion. A pericardial friction rub was heard on the fourth hospital day and persisted for four days. The patient was asymptomatic eight days after admission. He was maintained on anticoagulants for five weeks, and was gradually ambulated until discharged from the hospital six weeks after admission. Serial electrocardiograms revealed the evolving pattern of an acute extensive anterior myocardial infarction. The laboratory work and the chest roentgenogram were normal at the time of discharge. The discharge diagnosis was that of a myocardial infarction complicated by pericarditis, pulmonary embolism, and pleural effusion.

From the Department of Research and Laboratories, National Jewish Hospital at Denver, and University of Colorado School of Medicine, Denver, Colo.

Received for publication Feb. 20, 1956.

*Present address: San Francisco Hospital, San Francisco, Calif.

**Present address: Robert Packer Hospital, Sayre, Pa.

He felt well for one week when he experienced pressure over the anterior chest. This was aggravated by deep breathing, coughing, and turning from one side to another. There was no radiation of the pain. There was no hemoptysis or dyspnea. The physical examination was normal. The white blood count was 5,000 cells per cubic millimeter with a normal differential count. The erythrocyte sedimentation rate was 9 mm. per hour. An electrocardiogram showed

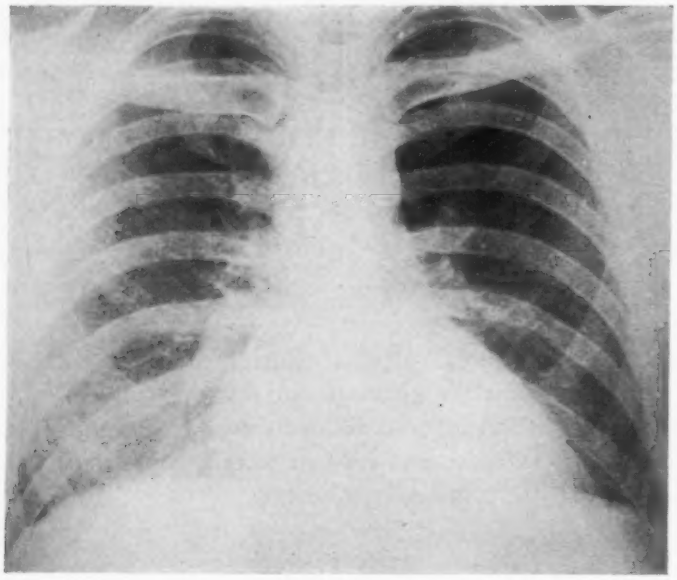


Fig. 1.—Chest roentgenogram on day preceding second hospital admission shows increase in cardiac silhouette.

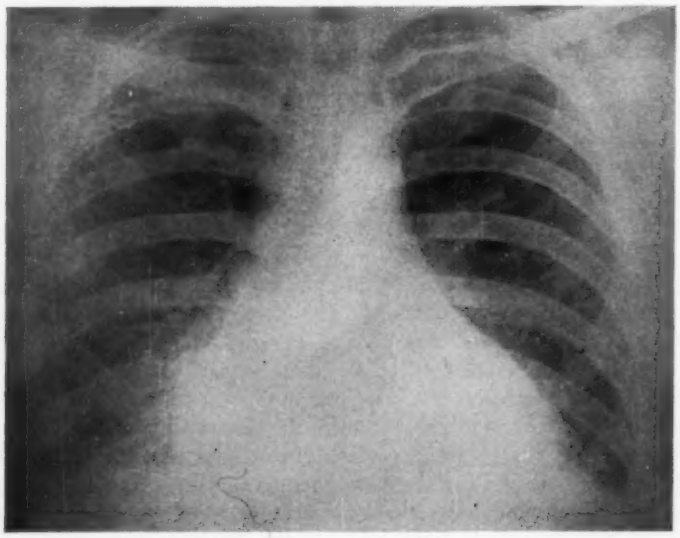


Fig. 2.—Chest roentgenogram on day of second hospital admission shows further increase in the cardiac silhouette with blunting of both costophrenic angles.

no change from that taken one week previously. The chest roentgenogram (Fig. 1) was normal except for increase in cardiac silhouette when compared with past films. One day later his symptoms recurred and were now associated with chilliness, aching, and slight temperature elevation. He was readmitted to the hospital eight days after discharge and fifty days after his first admission.

Physical examination revealed an apprehensive white man whose blood pressure was 138/78 mm. Hg, pulse 112 per minute, and respiratory rate 22 per minute. His skin was warm and moist. There was no distention of the cervical neck veins. There was dullness to percussion, diminished tactile fremitus, diminished breath sounds, and diminished vocal resonance over the

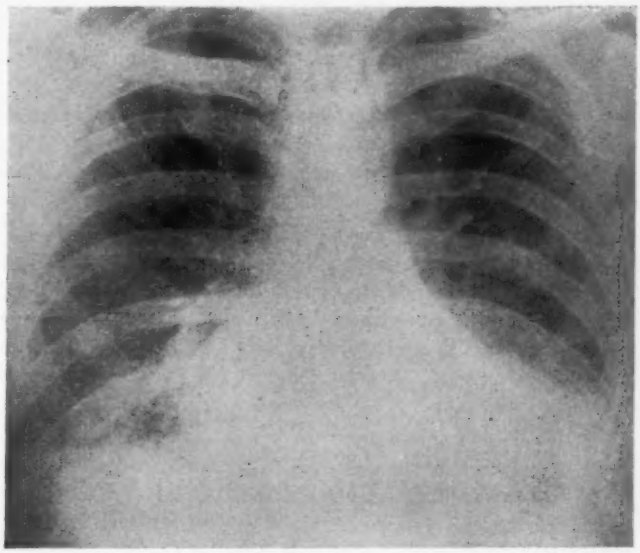


Fig. 3.—Chest roentgenogram taken four days after second hospital admission shows increased obliteration of the left costophrenic angle.

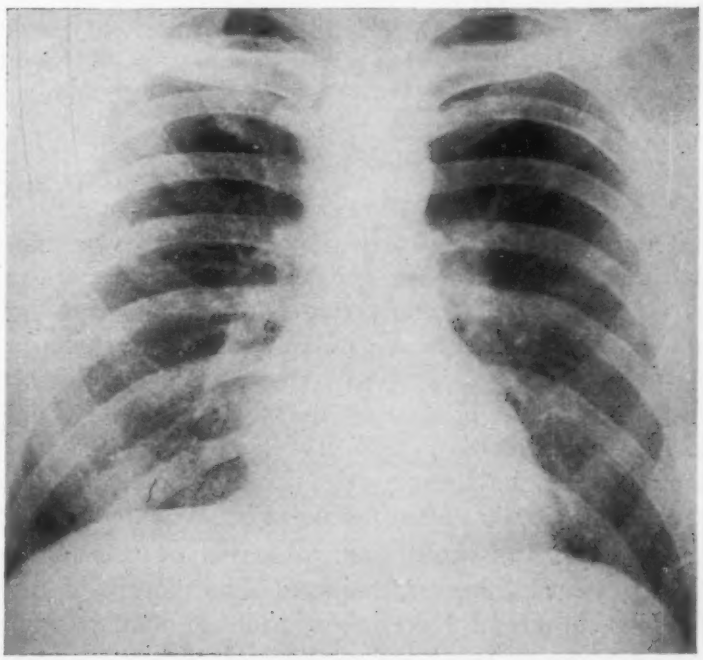


Fig. 4.—Chest roentgenogram taken five weeks after second hospital admission shows no abnormalities.

right lower lung field posteriorly. Râles were not heard. The examination of the heart was normal except for sinus tachycardia. The white blood count was 8,000 cells per cubic millimeter with a normal differential count. The prothrombin time and the bleeding and clotting times were normal. An electrocardiogram revealed no change from that taken one day previously.

A chest roentgenogram (Fig. 2) revealed blunting of both costophrenic angles as well as further increase in cardiac size when compared to that taken the day before. The following day, the erythrocyte sedimentation rate was 23 mm. per hour. Fluoroscopic examination showed generalized diminished cardiac pulsations. In the supine position, there was widening of the supracardiac area with partial obliteration of the aortic arch. Two days later, the chest roentgenogram revealed increased obliteration of the right costophrenic angle. A right thoracentesis was performed and 1,000 c.c. of straw-colored fluid was removed. This had a specific gravity of 1.013, and contained 1,000 cells per cubic millimeter, 92 per cent of which were lymphocytes. A chest roentgenogram (Fig. 3) taken four days after the second admission revealed increased pleural effusion on the left side. A left thoracentesis was performed and 400 c.c. of straw-colored fluid removed. This had a specific gravity of 1.016 and contained 300 cells per cubic millimeter, 87 per cent of which were lymphocytes.

The patient had a low-grade temperature elevation for the first five days of the second hospitalization. He was moderately ill and uncomfortable for eleven days, complaining of aching in the chest aggravated by motion. Transient pleural friction rubs were heard for ten days. He was treated with antimicrobial agents for ten days. There was no weight loss nor diuresis following the intramuscular injection of 2 c.c. of mercuhydrin daily for three days. Following the tenth day of hospitalization, he began to improve. A chest roentgenogram taken twenty days after admission showed pleural thickening and blunting of both costophrenic angles. The cardiac silhouette was now almost normal in size.

During the second hospitalization weekly chest roentgenograms, blood counts, erythrocyte sedimentation rates, and electrocardiograms were done. The erythrocyte sedimentation rate remained elevated for three weeks. The white blood and differential counts were normal. The electrocardiogram remained unchanged. The final chest roentgenogram (Fig. 4) was normal. The cold agglutination and heterophile antibody titers, the blood urea nitrogen, blood and throat cultures, and smears for lupus erythematosus cells were negative. The first and second strength PPD, as well as the histoplasmin and the coccidin skin tests were negative. Specimens from the pleural effusion revealed no organisms on smear, culture, or guinea pig inoculation, and were negative for tumor cells. Three stool specimens were negative for ova and parasites.

The patient has remained well during the year of follow-up examinations.

DISCUSSION

The simultaneous occurrence of bilateral pleural effusion with pericardial effusion is an uncommon clinical experience. Among the many causes for bilateral pleural effusion, there are few associated with pericardial effusion; of the causes for pericardial effusion, there are few associated with bilateral pleural effusions. Congestive heart failure, lupus erythematosus, carcinomatosus, and tuberculosis have produced these findings. When present, they occur in the advanced stages of the disease. Despite intensive study, no cause was found for the polyserositis in this patient. The differential diagnosis of the conditions which may be present when pleural or pericardial effusions occur after myocardial infarction has been discussed by Wolff.[1]

Many characteristics of the disease presented by this patient are similar to those following mitral commissurotomy.[2] The picture of the postcommissurotomy syndrome is one of fever, chest pain aggravated by breathing and motion, cough, dyspnea, pleural and pericardial effusion, pneumonitis, leukocytosis, elevated erythrocyte sedimentation rate, congestive heart failure, cardiac arrhythmia, and electrocardiographic changes suggestive of pericarditis. These findings have occurred as soon as twelve days after operation and may recur for as long as eighteen months. It has been reported in between 25 to

40 per cent of patients having this operation. The cause for the syndrome is not known, but it may represent a recurrence of acute rheumatic fever or may be a reaction to cardiac trauma. The attacks are usually self-limited and persist for six to eight days, but may be as short as two days or persist for weeks. When pleurisy occurs it is usually unilateral and not large enough to require thoracentesis.

Dressler[3] has stressed the similarities between idiopathic pericarditis and the postcommissurotomy syndrome. He has also reported[4] a febrile complication of myocardial infarction that resembled idiopathic pericarditis and the postcommissurotomy syndrome. This present case had some clinical features resembling those presented in these two reports.

Hemopericardium due to anticoagulant therapy[5] has been reported following myocardial infarction. This is most unlikely in this case because the prothrombin time was normal on discharge and on readmission. In addition, there have been no reports of pleural effusion due to anticoagulant therapy.

A dissecting aortic aneurysm has been known to have produced myocardial infarction as well as pericardial and pleural effusion. The pleural effusion when it occurs is usually unilateral, hemorrhagic, and occupies the left hemithorax. The benign nature of the disease in our patient and the follow-up for one year tends to rule out this diagnosis.

McKinley[6] reported one patient with serum sickness who had a cardiac enlargement, pericarditis, and pleurisy as part of an anaphylactic response. Zivitz[7] reported another case of polyserositis due to serum sickness. There was no evidence for an allergic or hypersensitive state as the cause for the disease in this patient.

SUMMARY

A case of bilateral pleural effusion with pericardial effusion of unknown cause occurring seven weeks after a myocardial infarction is reported. The similarity of the clinical and laboratory findings to those of the postcommissurotomy syndrome are noted. Possible causes for the effusions are discussed.

REFERENCES

1. Wolff, L.: New England J. Med. **244**:965, 1951.
2. Elster, S. K., Wood, H. F., and Seely, R. D.: Am. J. Med. **17**:826, 1954.
3. Dressler, W.: Am. J. Med. **18**:591, 1955.
4. Dressler, W.: Circulation **12**:697, 1955.
5. Lawrence, L. T.: Arch. Int. Med. **96**:757, 1955.
5a. Dressler, W.: J. A. M. A. **160**:1379, 1956.
6. McKinley, C. A.: J. Lancet **68**:61, 1948.
7. Zivitz, N., and Oshlag, J. A.: J. Allergy **20**:136, 1949.

SIMULTANEOUS ELECTROCARDIOGRAMS IN THORACOPAGUS TWINS

NORMAN J. JOHNSON, M.D., AND JAMES E. DOHERTY, M.D.

LITTLE ROCK, ARK.

SEVERAL reports of thoracopagus twins, well studied from the anatomic standpoint, appear in the literature, but to our knowledge only one report[1] of simultaneous electrocardiograms in such infants has appeared. It is the purpose of the present communication to report simultaneously recorded electrocardiograms in a pain of thoracopagus twins.

CASE REPORT

C. J. and B. J., Negro female thoracopagus twins, were admitted to the University Hospital on July 29, 1954, at the age of 4 days. They had been born to a 38-year-old father and a 26-year-old mother who were in good health. There had been three previous pregnancies, the first two resulting in single births of normal, full-term infants and the third resulting in twins, one a boy and the other a girl. The pregnancy had been entirely uneventful and the mother's health had been good throughout. The conjoined twins were delivered in the home without difficulty and apparently at term. Their combined weight was 9 pounds 12 ounces at birth. It was noted that they breathed immediately and no cyanosis was observed.

Physical Examination.—These 4-day-old thoracopagus twins were intimately joined from the manubrium sterni to the umbilicus, a distance of 11½ cm. The attachment at the manubrium appeared to be bony. The rib cages were separate. Both infants held their heads in a position of opisthotonos. They did not appear acutely ill and were in no distress. There was a single umbilicus which was common to both twins. It was impossible to palpate or visualize the point of maximal cardiac impulse. Heart tones were best heard at about the midline of the chest in both twins. They both had a regular sinus tachycardia at the same rate. No murmurs were heard. After the first few hospital days both twins had occasional episodes of cyanosis limited to the hands and feet. B. J. frequently had respiratory rates as high as 120 per minute; C. J. never above 50 per minute.

Course in Hospital and Laboratory Data.—In order to determine the feasibility of separating the twins, several studies were performed. Intravenous pyelograms showed at least one functioning kidney in each twin with some passage of contrast media from one twin to the other. Barium enema and upper gastrointestinal series were interpreted as revealing entirely separate normal gastrointestinal tracts. Angiocardiograms revealed what was thought to be a three-chambered heart in B. J. with either a two- or three-chambered heart in C. J. The hearts appeared to be intimately fused, some contrast material passing from a single ventricle in one twin directly into a single ventricle in the other. The single ventricle in each twin gave rise to a common trunk which divided into two main arterial trunks. One of the main arterial trunks of B. J. supplied the head, neck, and pulmonary circulation, while the other supplied the thoracic aorta and ab-

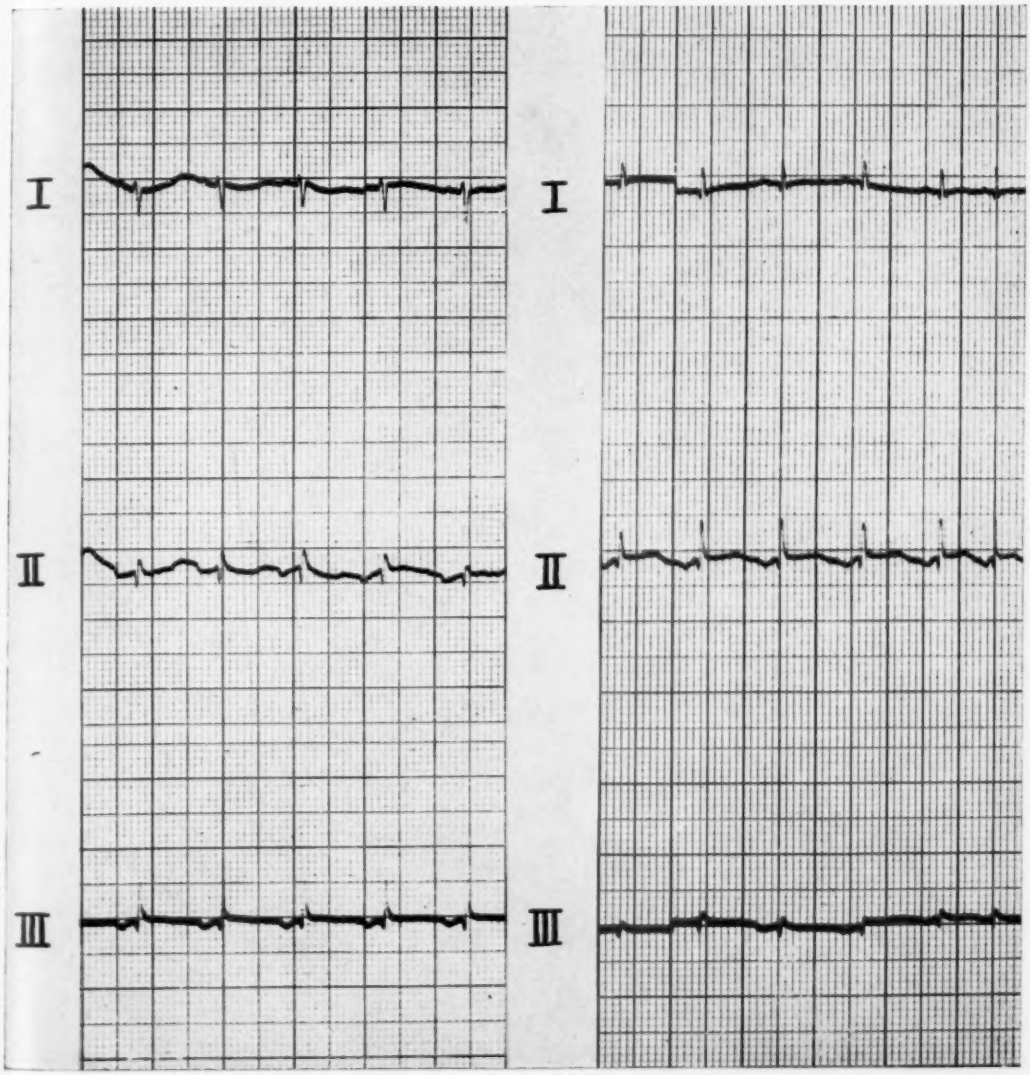
From the Departments of Pediatrics and Medicine, University of Arkansas School of Medicine, Little Rock, Ark.

Study of these patients was assisted by a grant from Arkansas Heart Association.

Received for publication March 26, 1956.

dominal aorta and the remainder of the systemic circulation. The common trunk of C. J. divided into the pulmonary artery and the aorta. The hepatic veins communicated freely and there appeared to be intimate fusion of the two livers.

After a two-month hospital stay during which cyanosis and rapid respirations featured the course of both infants, an attempt was made at surgical separation. The decision to attempt separation of these twins was felt justified because of their desperate condition and the opinion



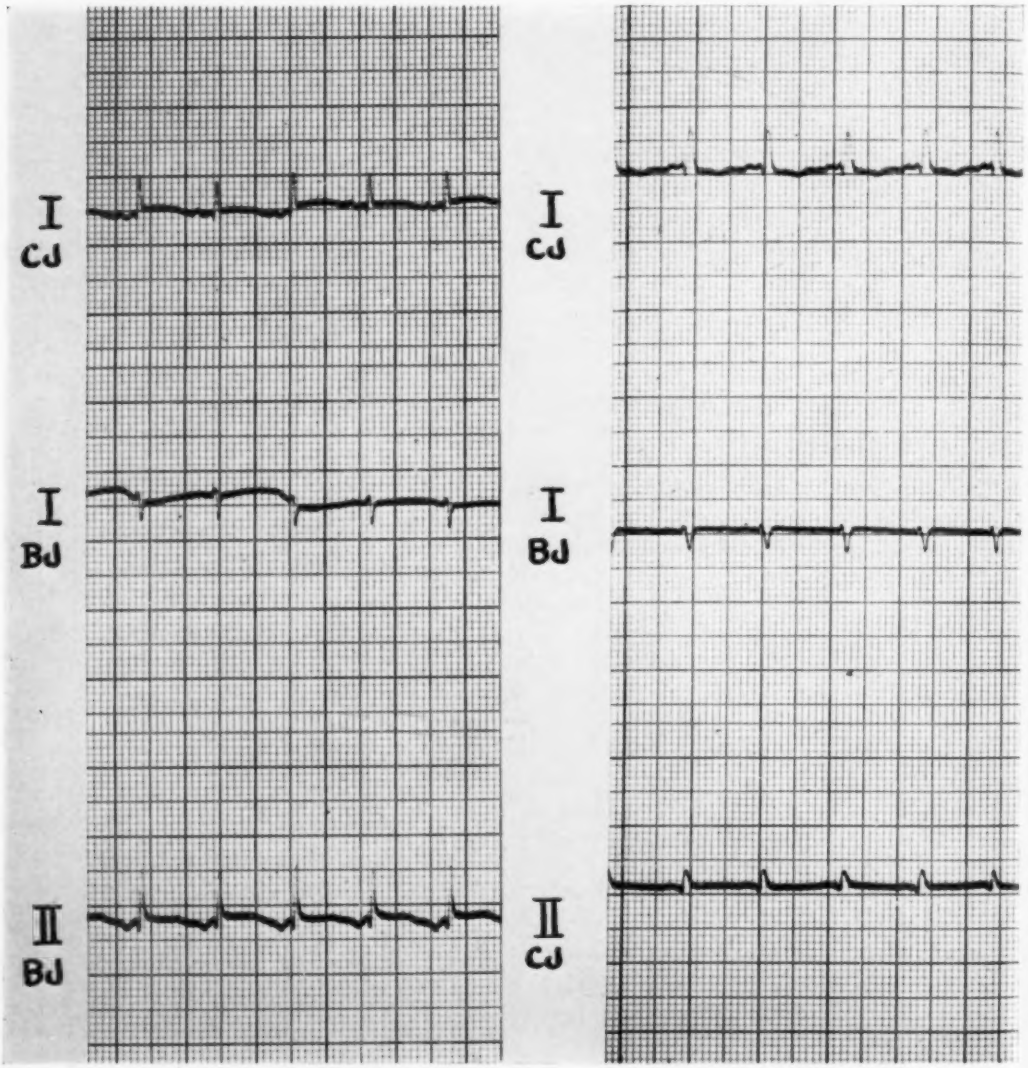
A. *B.*

Fig. 1.—Routine standard limb Leads I, II, and III. *A*, B. J. and *B*, C. J.

that they would not survive if they remained conjoined. It was hoped that despite the intimate association of the hearts, demonstrated by electrocardiograms and angiocardiograms, perhaps one of the individuals might be saved if a surgical procedure were successful. The two livers were dissected from one another, but the hearts were too intimately fused for surgical separation and both twins succumbed during the procedure. The anatomic findings confirmed the angiocardiographic observations described above.

DISCUSSION

Leads I, II, and III were recorded simultaneously on both patients (Fig. 1). An obvious difference between the tracings was observed. B. J. demonstrated right axis deviation, while in C. J. the electrical axis was left. Both individuals had T waves inverted in standard Leads II and III and low but upright T waves in Lead I. The QRS duration was about 0.05 second. The P-R interval was

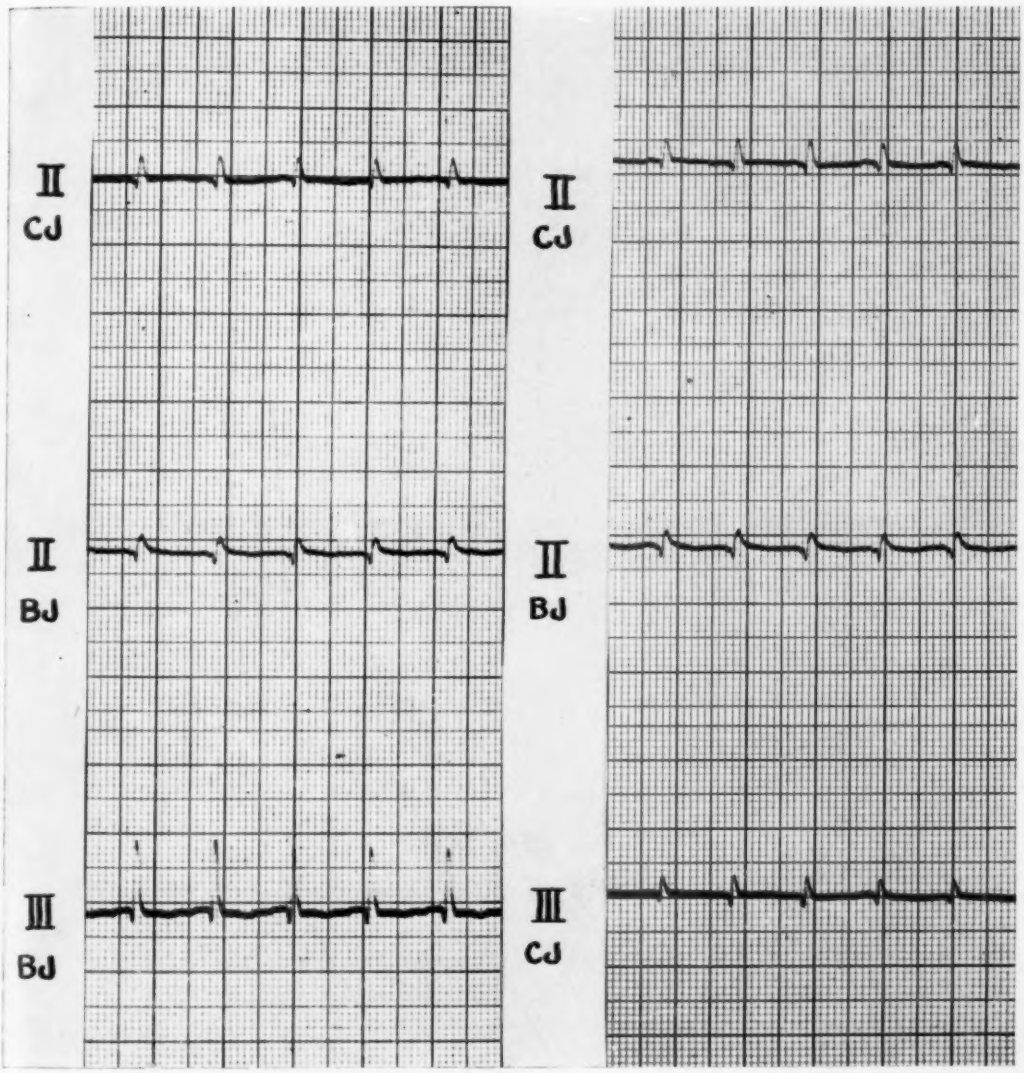


A. *B.*

Fig. 2.—Simultaneous leads on thoracopagus twins. *A*, Lead I, C. J.; Lead I, B. J.; Lead II, B. J.; and *B*, Lead I, C. J.; Lead I, B. J.; Lead II, C. J.

about 0.10 second in both individuals. Leads were recorded simultaneously on the twins (Figs. 2 to 4), which demonstrate a common focus of electrical activity for both hearts. There was no difference in the onset of auricular or ventricular electrical systole in either patient on the simultaneous leads, and the impulses resulting from the simultaneous depolarization would seem to be a summation

of the electrical forces of both hearts. No precordial leads were obtained because of the thoracic anomaly. A unipolar lead was placed in the right scapular area of each twin and leads were recorded simultaneously (Fig. 4). The mean electrical force is directed anteriorly in C. J. and posteriorly in B. J. Fig. 5 shows an interesting superimposition of electrical axis of the two patients. Upon inspecting this figure recall that the twins faced each other. By preparing frontal plane



A. *B.*

Fig. 3.—Simultaneous leads on thoracopagus twins. *A*, Lead II, C. J.; Lead II, B. J.; Lead III, B. J.; and *B*, Lead II, C. J.; Lead II, B. J.; Lead III, C. J.

QRS vectors in the usual fashion (Fig. 5*A*), we found that the QRS axes were exact mirror images and that by placing the figures face to face (Figs. 5*B* and 5*C*), the axes could be superimposed. A common site of impulse formation was present, thus differing from the other published case (Aird, 1954) of simultaneous

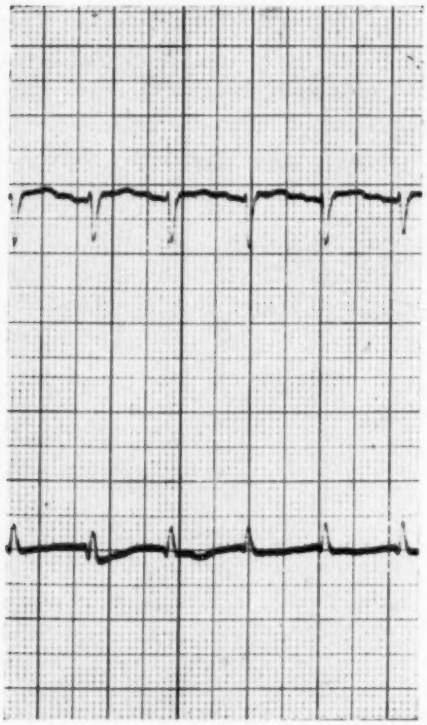
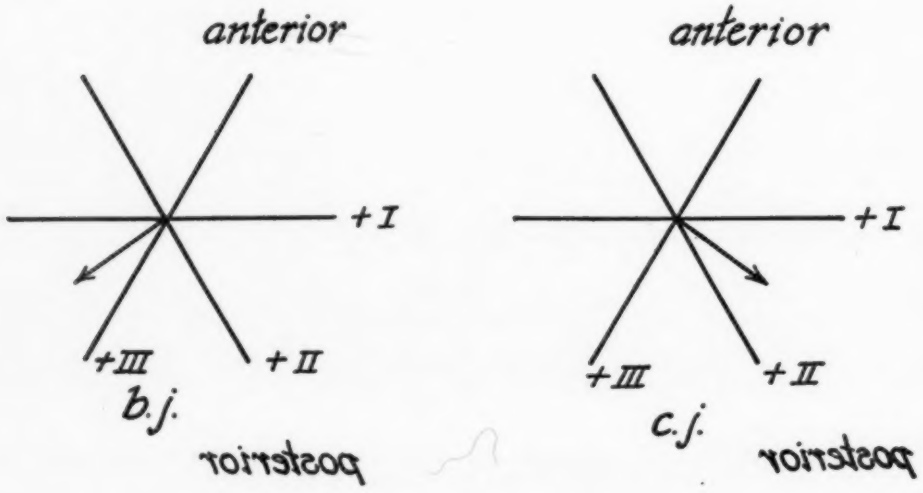
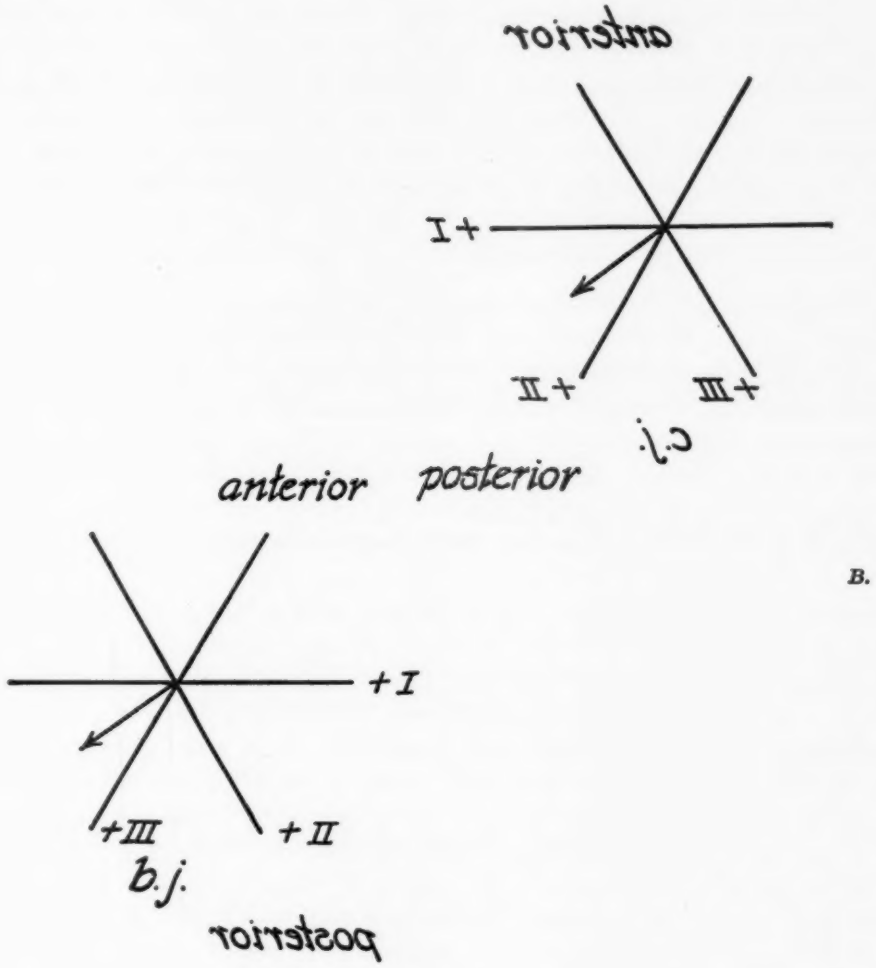


Fig. 4.—Simultaneous leads on thoracopagus twins. Unipolar lead from right scapular region in C. J. (above) and B. J. (below).

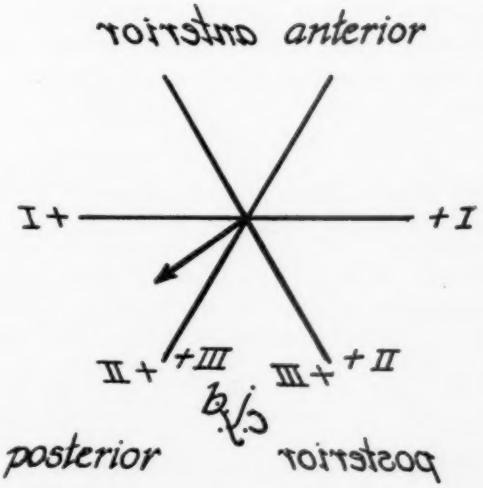


A.

Fig. 5.—Superimposition of frontal plane electrical axes. *A*, separate QRS axes on B. J. and C. J. *B*, figures above placed "face to face" as in life. *C*, figures superimposed as one mean QRS electrical force. (*Cont'd on opposite page.*)



B.



C.

Fig. 5.— Cont'd. *B* and *C*. *(For legend see opposite page.)*

electrocardiograms in thoracopagus twins, where the electrical activity of the hearts was shown to be independent. Because of the intimate association of the hearts and the simultaneous electrical activity, the reported similarity of electrocardiograms in identical twins[2] was not present in these individuals. It has been pointed out by Aird[1] that, although thoracopagus twins are usually assumed to be monovular, due to fission of the embryo, they often differ from each other more than do separate monovular twins. He also points out that there is usually some "mirror imaging" represented as some degree of situs inversus viscerum.

SUMMARY

Simultaneous electrocardiograms on thoracopagus twins have been presented. These demonstrate a single focus of electrical activity for both hearts.

REFERENCES

1. Aird, Ian: Brit. M. J. **1**:831-837, 1954.
2. Parade, G. W., and Lehmann, W.: Ztschr. f. menschl. Vererb.-u. Konstitutionslehre **22**:96-104, 1938.

LÖFFLER'S ENDOCARDITIS PARIETALIS FIBROPLASTICA WITH EOSINOPHILIA

MORTON J. WIENER, M.D., AND EDWIN M. KNIGHTS, JR., M.D.

DETROIT, MICH.

AN UNUSUAL case of endocarditis characterized by a very high eosinophilia and a progressive, refractory congestive heart failure was described in 1955 by Hoffman, Rosenbaum, and Genovese.[1] They believed that this was the first such case reported in the medical literature of the United States and the ninth such case reported in all medical literature. A complete review of all previous cases of this entity was presented. Lennox,[2] in 1948, reported from London a case associated with status asthmaticus which he felt was the earliest example of this condition and which gave further evidence for the allergic origin of Löffler's endocarditis. Löffler of Zurich described transient lung infiltrations with eosinophilia in 1932 and in 1936 described a syndrome of parietal endocarditis with eosinophilia. The six cases reviewed by Lennox described congestive heart failure with eosinophilia. The heart failure is progressive and usually associated with ascites, edema, and enlarged liver. The heart is often not enlarged. Eosinophilia is sometimes very high. Buchler's case showed a constant eosinophilia which went as high as 35,900 per c. mm. Post-mortem findings are that of massive endocardial fibrosis and extensive mural thrombosis of both ventricles. The lesions were different from the cardiac lesions of asthma.

Forty cases of cardiovascular collagenosis with parietal endocardial fibrosis were reported in 1953 from Johannesburg, South Africa, by Becker, Chatgidakis, and van Lingen.[3] They felt that these cases were related to Löffler's endocarditis parietalis fibroplastica. They produced evidence to show that the condition was due to disturbances of the connective tissues of the heart. It should accordingly be classified as a diffuse collagen disease along with periarteritis nodosa, lupus erythematosus, diffuse scleroderma, and rheumatic heart disease. However, only one of the cases reported showed a marked absolute eosinophilia.

CASE REPORT

A 45-year-old Negro was first seen by one of us (M.J.W.) in the office on Sept. 11, 1950. He complained of a chest cold which had been present for one year, but lately the cough was productive of a stringy sputum and was worse at night. He was a factory worker whose working environment was smoky. He tried various medicine with no relief. There was no history of heart trouble and no hemoptysis. He had lost twenty pounds in the previous year. He smoked a pack of cigarettes per day and took an occasional alcoholic drink. His mother was living and well. His father died of kidney trouble at an early age. Two brothers were dead of unknown causes, and three brothers and two sisters were living and well. He was separated from his wife. There were no animals about the house.

From the Departments of Internal Medicine and Pathology, Harper Hospital, Detroit, Mich.
Received for publication March 19, 1956.

The patient was in mild respiratory distress. The temperature was normal, and the pulse was 110 per minute and regular. The nasal mucous membranes were swollen and edematous. There was a loud, rough systolic murmur over the precordium. The heart size was normal. There was no peripheral edema, and the liver was not palpable. There were inspiratory and expiratory wheezes throughout both lung fields, and moist râles were present in the right base. The lymph nodes were enlarged.

Chest x-ray and electrocardiogram were normal. Serology was negative. The urine showed no albumin or sugar and there were a few hyaline casts and red blood cells in the sediment. The red blood count and hemoglobin content were normal. The white blood count was 22,100 per c. mm. with 27 per cent lymphocytes, 2 neutrophils, 1 monocyte, and 70 eosinophiles. A preparation for sickling was negative.

It was felt that this was an allergic condition as well as cardiac. He was digitalized and given antihistamines and iodides. Adrenalin would give some relief, and mercuhydrin would cause diuresis and improve the dyspnea.

He was referred to a hematologist who felt that this might be a case of congenital eosinophilia or trichinosis. A trichinella skin test was negative. A brother's blood was examined and was normal.

He was admitted to Harper Hospital on Nov. 22, 1950. A complete allergic work-up was negative. Repeated stool examinations revealed no parasites. Serum proteins were normal. A tuberculin test was negative. The bone marrow was normal except for hyperplasia of the eosinophilic elements. Platelets were normal. Skin and muscle biopsies were normal. The sedimentation rate (Westergren) was 6 mm. per hour. The white blood count was checked on many occasions and was elevated with a high eosinophile count. On one occasion, the white blood count was 41,000 per c. mm. with 91 per cent eosinophiles. A Thorn test with 25 mg. of corticotropin intramuscularly caused a total eosinophile count of 15,375 to be depressed to 13,750 in four hours.

He had been admitted to Harper Hospital on four occasions, but managed to keep at his job between admissions with the aid of digitoxin, mercuhydrin, Adrenalin, and antihistamines. His spells of dyspnea would be ushered in by bouts of sneezing. Pruritis began in July of 1951 and was persistent. Gallop rhythm and cardiac enlargement became apparent in April of 1952. He developed pneumonia in September of 1952. With this the white blood count was 7,900 per c. mm. with 39 per cent eosinophiles, and there was 14 per cent stabs and 33 segmented granulocytes. Usually there were less than 4 per cent neutrophiles. When the pneumonia cleared, the neutrophiles again disappeared and the eosinophiles increased. The heart which was enlarged before the pneumonia returned to normal size and the murmur became less intense. A culture for tubercle bacilli was negative.

He had returned to work following the pneumonia but became progressively weaker. In February, 1953, 12½ mg. of cortisone four times a day was added to the medication. Ten days later the lungs were full of moist râles and there were signs of abdominal fluid. Cortisone was discontinued. Mercuhydrin and ammonium chloride gave him some relief. He was admitted to Harper Hospital on Feb. 17, 1953. The blood count taken on the following morning, a few hours before the patient's death, showed a white blood count of 15,300 per cubic millimeters with 31 per cent eosinophiles, 35 segmented polys, and 12 stabs.

Post-Mortem Findings.—Necropsy revealed the body of a well-developed, well-nourished Negro with no abdominal distension nor evidence of peripheral edema. The liver was palpable two fingerbreadths below the right costal margin.

On opening the thoracic cavity, the left lung was adherent to the parietal pleura throughout its entire surface and the right lung was adherent on its posterior surface.

The heart appeared moderately enlarged and weighed 410 grams. An average amount of fluid was found in the pericardial sac. There was marked dilatation of the right atrium and ventricle. Upon opening the heart, there was found to be thrombosis of the right atrium and particularly in the auricular appendage. On sectioning, this appendage was found to be thrombosed throughout its entire lumen. The right ventricle contained a mural thrombus averaging 1.0 to 1.5 cm. in thickness. There were no visible areas of discoloration and no palpable softening of the myocardium was found. The left ventricular cavity contained no thrombi; however, mural

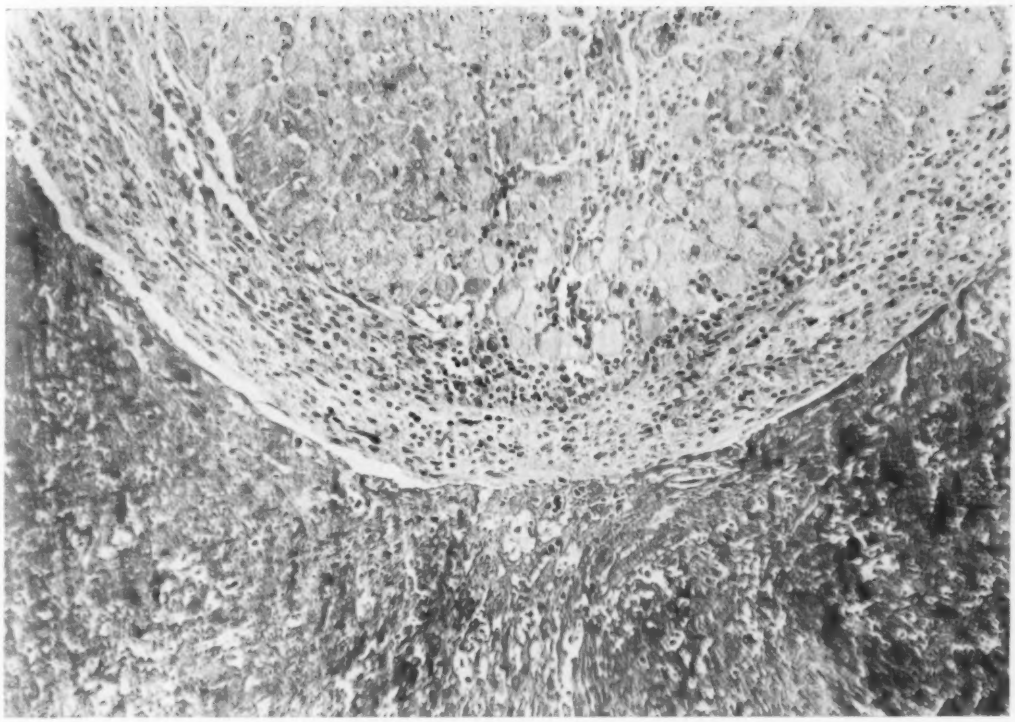


Fig. 1.—The endocardium is markedly thickened and is the site of a diffuse inflammatory process which extends into the underlying myocardium. A fresh mural thrombus adheres to the endocardium; in other areas this showed beginning organization. (Magnification × 100; reduced 2/9.)

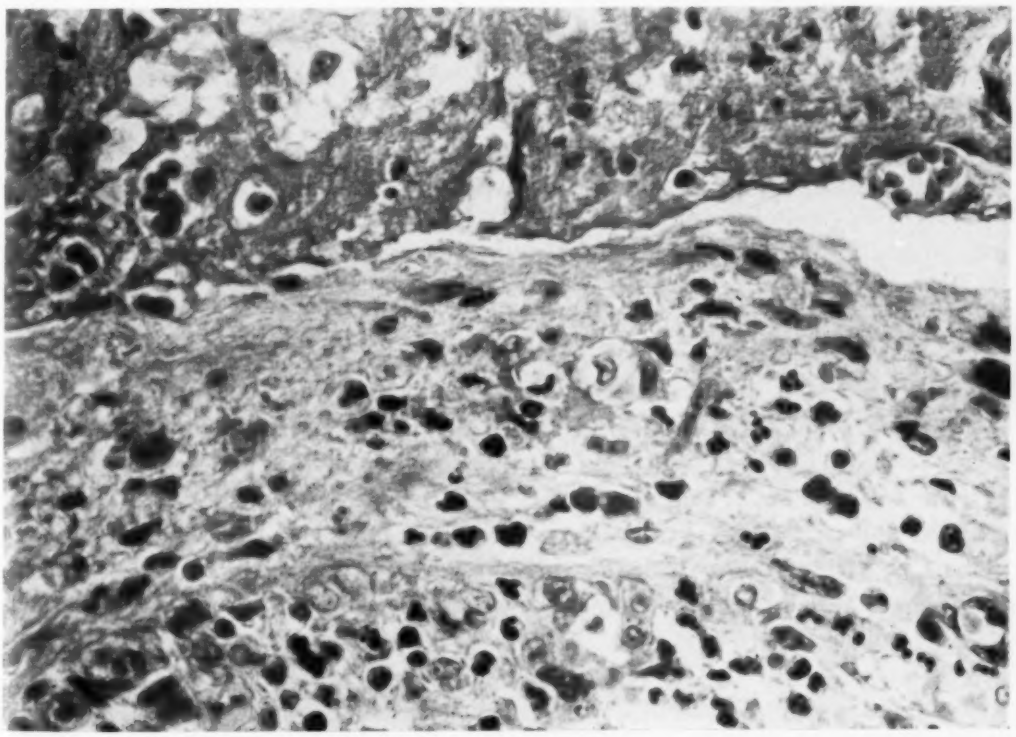


Fig. 2.—Higher magnification reveals the mixed nature of the inflammatory cells within the thickened endocardium; neutrophiles, eosinophiles, lymphocytes, and macrophages are found. These cells are also seen in considerable numbers within the myocardium. A fresh mural thrombus is also seen. (Magnification × 430; reduced 2/9.)

thrombi were adherent to the left atrium and filled the left auricular appendage. The chordae tendineae of the mitral valve were shortened and thickened and a single firm nodule was found near the free margin of the mitral valve. Both the aortic and pulmonary valves appeared within normal limits except for slight thickening and calcification of the aortic cusps. The coronary arteries showed no abnormalities.

The lungs, liver, and spleen showed gross evidence of chronic passive congestion. No periarteritis nodosa was found, nor was there any evidence of systemic parasitic infection.

Microscopic study of the heart showed the predominating changes to be those of subendocardial fibrosis, diffuse endocarditis, and mural thrombus formation. These changes were found in the atria, a semilunar valve, and in the ventricular walls. The inflammatory infiltrate was mixed in type, including large numbers of polymorphonuclear cells and some eosinophils within the endocardium, myocardium, and some portions of the epicardium. The valves were also the site of fibrosis and some foci of fibrinoid change (Figs. 1 and 2). The auricles showed hypertrophy of the myofibrils. No Aschoff nodules were encountered. Blood vessels showed no hypertrophy nor occlusion. The mural thrombi appeared to be fairly recent in origin, showing lamination and occasional small areas of organization adjacent to the endocardial surface. One small fibrin deposit was found on the endocardium.

Sections of other organs showed the typical findings of chronic passive congestion of the lungs, liver, and spleen. No vascular abnormalities were found. The kidneys showed acute congestive changes, plus focal cortical accumulations of polymorphonuclear neutrophils and eosinophils. Striated muscle sections showed no parasitic involvement.

COMMENT

This case, presumably the second of its kind to be reported in the medical literature of the United States, is one which fulfills the criteria of Löffler's endocarditis parietalis fibroplastica with eosinophilia. The progressive, relentless cardiac failure was present and persisted until death in spite of medication. There were definite allergic manifestations such as sneezing, wheezing, and pruritis present in this case. The eosinophilia was striking and on one occasion reached 40,400 eosinophils per c. mm. (a white blood count of 41,000 with 91 per cent eosinophils).

It is of interest to note that although a Thorn test with only 25 mg. of corticotropin given intramuscularly caused no appreciable fall in the total eosinophil count, the alarm reaction caused by the acute pneumonitis and later by the terminal episode resulted in a fall of the eosinophils and total white blood count and a marked rise in the neutrophil count.

Although there is endocardial thickening in this condition, this is not the same disease as endocardial fibroelastosis in which there is fibrous and elastic tissue thickening of the endocardium without evidence of inflammation. This latter condition is probably due to a congenital or developmental defect.[4]

Ampuran[5] believes that Löffler's syndrome can affect any tissue of the body from the superficial skin and scalp to the brain, heart, or pancreas. He is also inclined to believe that a transition from a readily reversible to a less easily reversible or even an irreversible hypersensitive histologic sequence (as demonstrated by the experiments of Arthus) can and does occur in some cases of this disease.

The changes in the chordae tendineae with thickening of the valves and a nodule in the mitral valve could be due to an old rheumatic carditis. The marked

subendocardial fibrosis, diffuse endocarditis, mural thrombus formation, and the absence of Aschoff nodules point to another pathologic process.

While it is easy to understand why progressive failure occurs because of the thickening of the endocardium, the etiology of this condition is obscure. Perhaps earlier in the course of this condition steroids would have been beneficial. When steroids were given in this case the changes were undoubtedly irreversible.

SUMMARY

A case of Löffler's endocarditis parietalis fibroplastica is presented. Clinically there are many features which suggest an allergic etiology. Pathologically there are a few changes compatible with a rheumatic carditis, but a marked subendocardial fibrosis and mural thrombus formation suggests a different process. The steroids used late in the course might have been beneficial if used earlier in the disease.

REFERENCES

1. Hoffman, F. G., Rosenbaum, D., and Genovese, P. D.: Ann. Int. Med. **42**:668, 1955.
2. Lennox, B.: J. Path. & Bact. **60**:621, 1948.
3. Becker, B. J. P., Chatgitdakis, C. B., and van Lingen, B.: Circulation **8**:345, 1953.
4. Golper, M. N.: Radiology **61**:685, 1953.
5. Ampuran, J. C.: J. A. M. A. **151**:65, 1953.

ADDENDUM

Since the writing of this paper there has appeared a report of a case of endocardial fibrosis simulating constrictive pericarditis. There was a blood eosinophilia and pathologic characteristics which indicate that this is another case of Löffler's endocarditis parietalis fibroplastica with eosinophilia. (Clark, G. M., Valentine, E., and Blount, G., Jr.: New England J. Med. **254**:349, 1956)

It is with deep regret that the Editor announces the death on October 24, 1956, of Dr. Stanley Gibson, of Chicago, a member of the Editorial Board of the American Heart Journal; and on November 1, 1956, of Dr. G. Lyman Duff, of Montreal, a former member. Sincere sympathy is offered to their families and colleagues.

Book Review

ADVANCES IN INTERNAL MEDICINE. Edited by William Dock, M.D., and I. Snapper, M.D., Vol. 7, Chicago, 1955, The Year Book Publishers, Inc., 311 pages.

This volume contains eight review articles on various medical subjects. Of interest to the cardiologists is the section on diseases of the pericardium written by Drs. Victor A. McKusick and A. McGehee Harvey of the Johns Hopkins Hospital staff.

The authors have done an excellent job in reviewing the important literature up to date and have included a bibliography of 170 pages. Etiology, diagnosis, and treatment are considered in detail. A comprehensive classification of diseases of the pericardium is given early in the article.

A.C.D.

Announcement

THE COUNCIL ON POSTGRADUATE MEDICAL EDUCATION OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS will present the following POSTGRADUATE COURSES ON DISEASES OF THE CHEST during the period January to April, 1957:

Vanderbilt University, Nashville, Tenn., January 14 to 18;
Mark Hopkins Hotel, San Francisco, Calif., February 25 to March 1; and
Bellevue-Stratford Hotel, Philadelphia, Pa., April 1 to 5.

Tuition for each course is $75. The most recent advances in the diagnosis and treatment of chest diseases—medical and surgical—will be presented.

Further information may be obtained by writing to the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Ill.